



Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

- Determine the quantity of evidence available for a technology of interest.
- Identify any gaps in the evidence.
- Inform decisions on topics that warrant fuller assessment by Health Technology Wales (HTW).

Topic exploration report number:	TER467
Topic:	Photobiomodulation therapy for dry age-related macular degeneration
Summary of findings:	<p>Age-related macular degeneration (AMD) is the leading cause of vision loss in people over 50 years old. Dry AMD affects around 80% of people with AMD and there are currently no established treatments. Photobiomodulation (PBM) therapy has been proposed as a treatment for dry AMD. PBM uses near infrared spectrum light to stimulate cells of the retina and delay cell death.</p> <p>We identified one HTA, one systematic review and three peer-reviewed individual studies. Included studies were randomised controlled feasibility trials of PBM compared to sham or no treatment, or single arm studies. Follow-up varied between three and twelve months. There was some evidence of improvement in PBM treated eyes, but the randomised trials were underpowered to detect differences between PBM and control groups for most outcomes. Authors for the majority of included studies declared financial relationships with the manufacturer of the device used to deliver PBM. We identified no economic evaluations.</p> <p>The literature highlights the need for a greater body of evidence on the efficacy and cost-effectiveness of PBM therapy for dry age-related macular degeneration.</p>

Introduction and aims

Age-related macular degeneration (AMD) is an eye condition affecting the macula, which is the central part of the retina responsible for detailed vision. AMD is the leading cause of vision loss in people over 50 years old. There are two types of AMD, wet and dry. Wet AMD is more serious and results in rapid loss of vision, but treatments exist. Dry AMD affects around 80% of people with AMD and is caused by age-related thinning of the macula build-up of a protein called drusen and cell death. Vision loss is slow. There are currently no established treatments.

Photobiomodulation (PBM) therapy has been proposed as a treatment for dry AMD. PBM uses near infrared spectrum light from a laser, or light emitting diode, to induce a photochemical reaction within the cells of the retina which is thought to delay cell death. Valeda Light Delivery System by LumiThera was identified as a specific example of PBM therapy technology by the topic proposer.

Health Technology Wales researchers searched for evidence on PBM therapy for dry AMD.

Evidence overview

We identified one HTA, one systematic review and meta-analysis and three peer-reviewed individual studies.

Health Technology Assessment

Waugh (2018) conducted a systematic review and HTA which reviewed any treatments for dry AMD using any study design. Searches were conducted from 2005 to 13 July 2017. Two PBM studies were identified. Both were single-arm studies, with three-month follow-up. One study of multi-wavelength PBM included 24 participants (42 eyes). There was evidence of an increase in best corrected visual acuity, an increase in contrast sensitivity and a reduction in drusen volume. Another study was available as an abstract only and reported some improvement in best corrected visual acuity, pattern electroretinography (ERG) and retinol sensitivity which are measures of dysfunction. The review authors noted that further trials were underway.

Systematic reviews

Heinen (2021) conducted a Cochrane review and meta-analysis examining effectiveness and safety of PBM therapy for dry AMD. Included studies were randomised controlled trials comparing PBM to standard care, sham treatment, or no treatment. Searches were conducted up to 11 May 2020. Two studies were included, with a total of 90 participants (106 eyes). One study was an unblinded study which compared single wavelength PBM with no treatment, and one study (LIGHTSITE I) was a single centre double-blind sham-controlled study using multi-wavelength PBM. Outcomes at 12 months were best corrected visual acuity, contrast sensitivity, vision-related quality of life score, progression of AMD and conversion to wet AMD. There was no evidence reported for a difference in best corrected visual acuity for PBM when compared with sham or no treatment. There was some evidence that PBM treated eyes showed improved contrast sensitivity compared with sham treatment. No evidence of differences between PBM and sham treatment were found for health-related quality of life or visual function. There was no evidence for a clinical difference between groups in either study for conversion to wet AMD and inconclusive evidence that PBM compared with no treatment prevented progression of AMD. Certainty of evidence was low to very low. The review authors noted that the LIGHTSITE I study was underpowered for the primary outcome. They also

highlighted the need for agreement on the appropriate clinical and patient-reported outcome measures. Authors of the LIGHTSITE I study declared a conflict of interest.

Individual studies

We identified three additional peer-reviewed studies.

Burton (2023) conducted a multicentre double-blind sham-controlled feasibility study, LIGHTSITE II. The study evaluated safety and efficacy of PBM in dry AMD. Forty-four participants (53 eyes) received multi-wavelength PBM or sham treatment nine times over three to four weeks, at baseline, four months, and eight months. Primary outcome was change from baseline in best corrected visual acuity at nine months in PBM-treated eyes (n=32) and there was some evidence of improvement (2.30 ± 5.23 letter improvement, $p=0.02$). Secondary outcomes included best corrected visual acuity for sham-treated eyes, comparisons between groups and other patient-reported and imaging outcomes. There was no evidence found for a difference in eyes treated with PBM compared with sham-treated eyes. Authors reported that the study was underpowered to detect differences. Authors declared a conflict of interest, having either received funds from the manufacturer of the device used or were company employees.

Benlahbib (2023) conducted a single arm study in participants with dry AMD and signs of progression (20 eyes). Participants received two treatments per week for five weeks. Outcomes included best corrected visual acuity, microperimetry-scotopic testing, drusen volume, central drusen thickness, quality of life at baseline and six months. There was evidence for improvements in best corrected visual acuity, drusen volume, central drusen thickness and quality of life. One patient experienced an adverse event at six months. No conflict of interest was declared.

Siqueira (2021) conducted a single arm study in ten participants (10 eyes) with dry AMD who were treated with nine sessions of single wavelength PBM. Outcomes were best corrected visual acuity, retinal sensitivity, and characteristics of the correction area using fundus automated perimetry up to 16 weeks after treatment. There was evidence of improvement in best corrected visual acuity and visual field. No adverse events were reported. Conflict of interest was unclear.

Economic evidence

We identified no economic studies.

Ongoing studies

We identified two ongoing studies. One is being prepared for publication and one is not yet recruiting.

LumiThera is conducting LIGHTSITE III (NCT04065490), a double-blinded, sham-controlled multicentre study in participants with dry AMD. Thirteen-month interim results have been presented as a conference abstract (Munk 2022). One hundred participants (148 eyes) with dry AMD have been randomised. The abstract lacks detail but reports that PBM may offer a new treatment for patients with dry AMD. Authors declared a conflict of interest, having either received funds from the manufacturer of the device used or were company employees.

We also identified a planned double-blinded, sham controlled study (NCT05507840) in patients with dry AMD treated with PBM every six months for two years. The study aims to recruit 121 participants. Primary outcome is the percentage of patients that develop late AMD after three years follow-up. Estimated study completion data is December 1st, 2027.

Areas of uncertainty

The evidence for the specific technologies submitted by the topic proposer comes from small, underpowered, randomised controlled trials and single-arm studies. Further clarification is needed in the following areas:

- Efficacy and safety of PBM in adequately powered randomised controlled trials
- Efficacy and safety of single wavelength compared with multi-wavelength PBM
- Optimum treatment schedule and length of treatment
- The most appropriate clinical and patient-reported outcome measures for AMD
- The most appropriate length of follow-up
- Evidence for cost-effectiveness in clinical practice

Literature search results

Health technology assessments and guidance

Waugh N, Loveman E, Colquitt J, et al. (2018). Treatments for dry age-related macular degeneration and stargardt disease: A systematic review. *Health Technology Assessment*. 22(27): 1-167. doi: <https://doi.org/10.3310/hta22270>

Evidence reviews and economic evaluations

Henein C, Steel DHW. (2021). Photobiomodulation for non-exudative age-related macular degeneration. *Cochrane Database Syst Rev*. CD013029(5). doi: <https://doi.org/10.1002/14651858.CD013029.pub2>

Individual studies

Benlahbib M, Cohen SY, Torrell N, et al. (2023). Photobiomodulation therapy for large soft drusen and drusenoid pigment epithelial detachment in age-related macular degeneration: a single-center prospective pilot study. *Retina*. 06: 06. doi: <https://doi.org/10.1016/j.ophtaha.2006.08.015>

Burton B, Parodi MB, Jürgens I, et al. (2023). LIGHTSITE II Randomized Multicenter Trial: Evaluation of Multiwavelength Photobiomodulation in Non-exudative Age-Related Macular Degeneration. *Ophthalmology and Therapy*. 12(2): 953-68. doi: <https://10.1007/s40123-022-00640-6>

Siqueira RC, Belissimo LM, Pinho TS, et al. (2021). Short-Term Results of Photobiomodulation Using Light-Emitting Diode Light of 670nm in Eyes with Age-Related Macular Degeneration. *Photobiomodulation, Photomedicine, and Laser Surgery*. 39(9): 581-6. doi: <https://doi.org/10.1089/photob.2021.0005>

Ongoing research

Anca R. (2022). Photobiomodulation for Dry Age Related Macula Degeneration [NCT05507840]. *Clinical Trials Registraton*. Available at: <https://clinicaltrials.gov/ct2/show/record/NCT05507840> [Accessed 11th May 2023].

LumiThera. (2021). Study of Photobiomodulation to Treat Dry Age-Related Macular Degeneration (LIGHTSITE III). *Clinical Trial Registration* [NCT04065490]. Available at: <https://clinicaltrials.gov/ct2/show/NCT04065490> [Accessed 11th May 2023].

Munk MR, Gonzalez VH, Boyer DS, et al. (2022). LIGHTSITE III (Interim Analysis): Evaluation of Multiwavelength Photobiomodulation in Dry Age-Related Macular Degeneration Using the LumiThera Valeda Light Delivery System. *Investigative Ophthalmology and Visual Science*. 63(7): 379-F0210.

Proposed research question and evidence selection criteria (if selected)

Proposed research question	What is the clinical and cost effectiveness of photobiomodulation therapy for dry age-related macular degeneration?
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	Included	Excluded
Population	People with dry age-related macular degeneration	People with any other macular disease including wet age-related macular degeneration
Intervention	Photobiomodulation therapy (may also be called low-level laser light therapy)	Photodynamic therapy Subthreshold or thermal laser treatment
Comparison/ comparators	Sham treatment Any other treatment including antioxidant or zinc supplements or no treatment	
Outcomes	Visual acuity measures Contrast sensitivity Drusen volume / thickness Disease progression (severity grading or atrophic lesion size) Visual function measures (e.g., visual function questionnaire score) Reading speed Patient satisfaction and quality of life Resource use	
Study design	Peer-reviewed secondary evidence and primary studies	Grey literature

Date of search:	May 2023
Concepts used:	Valeda Light Delivery System; LumiThera; Photobiomodulation therapy; low-level laser therapy; dry age-related macular degeneration
HTW topic categorisation:	Eye