

SUPPLEMENTARY MATERIALS

Photobiomodulation for Central Nervous System Disorders:

A Comprehensive Systematic Review of Delivery Routes, Mechanisms, and Clinical Evidence

Contents

Supplementary Material S1: List of Abbreviations (128 entries)
Supplementary Material S2: Complete Search Strategies for All Databases
Supplementary Material S3: PRISMA 2020 Checklist
Supplementary Table S1: Complete Characteristics of All Included Studies (n = 27)
Supplementary Table S2: Individual Study Risk of Bias Assessments (RoB 2 / ROBINS-I)
Supplementary Table S3: GRADE Evidence Profile — AD High-Irradiance PBM (≥ 20 mW/cm²)
Supplementary Table S4: GRADE Evidence Profile — AD Low-Irradiance PBM (< 10 mW/cm²)
Supplementary Table S5: GRADE Evidence Profile — AD intra-nasal-Containing Protocols
Supplementary Table S6: GRADE Evidence Profile — Parkinson's Disease
Supplementary Table S7: GRADE Evidence Profile — Acute Ischaemic Stroke (808 nm Laser)
Supplementary Table S8: GRADE Evidence Profile — Traumatic Brain Injury
Supplementary Table S9: Complete Dosimetry Parameters for All Studies
Supplementary Table S10: Wavelength Distribution by Condition
Supplementary Table S11: Excluded Studies with Reasons (Full-Text Stage)
Supplementary Table S12: Trial Registry Search Results
Supplementary Figure S1: Risk of Bias Summary (RoB 2)

Supplementary Material S1. List of Abbreviations

All abbreviations used in the manuscript and supplementary materials are listed below in alphabetical order.

Abbreviation	Definition
40Hz	Forty hertz (gamma frequency, 40 oscillations per second)
5-HT	Serotonin (5-hydroxytryptamine)
808nm / 810nm / 1064nm	Wavelength designations in nanometres
A2A receptor	Adenosine A2A receptor
AD	Alzheimer's disease
ADHD	Attention deficit hyperactivity disorder
ADP	Adenosine diphosphate
AE	Adverse event
AMPK	AMP-activated protein kinase
ANS	Autonomic nervous system
ASD	Autism spectrum disorder
ATP	Adenosine triphosphate
Aβ	Amyloid-beta (amyloid beta peptide)
BDNF	Brain-derived neurotrophic factor
BLaER1	Bipotent lymphoid and erythroid progenitor cell line 1 (macrophage model)
BMI	Body mass index
BP	Blood pressure
CARS	Childhood Autism Rating Scale
CCI	Controlled cortical impact (TBI model)
CIU	Cytochrome c oxidase inhibitory unit
ClinVar	Clinical variant database (NCBI)
CNS	Central nervous system
CoBRAS	Cochrane Bias Risk Assessment Scale
COX-2	Cyclooxygenase-2
CTE	Chronic traumatic encephalopathy
CW	Continuous wave (laser/LED output mode)
CYP450	Cytochrome P450 enzyme family
DA	Dopamine
DAD	Disability Assessment for Dementia scale
DB-RCT	Double-blind randomised controlled trial
DLPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
DNA	Deoxyribonucleic acid
DOPAC	Dihydroxyphenylacetic acid (dopamine metabolite)
DRS	Dementia Rating Scale
EEG	Electroencephalography
EMG	Electromyography
ETC	Electron transport chain
fMRI	Functional magnetic resonance imaging
FNIRS / fNIRS	Functional near-infrared spectroscopy

Abbreviation	Definition
GABA	Gamma-aminobutyric acid
GFR	Glomerular filtration rate
GI	Gastrointestinal
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
GSH	Glutathione (reduced form)
H₂O₂	Hydrogen peroxide
HAMA	Hamilton Anxiety Rating Scale
HAMD	Hamilton Depression Rating Scale
HPA axis	Hypothalamic-pituitary-adrenal axis
HR	Heart rate
HRV	Heart rate variability
HSP	Heat shock protein
ILIB	Intravascular laser irradiation of blood
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
IL-10	Interleukin-10
IN	intra-nasal (delivery route)
iNOS	Inducible nitric oxide synthase
IR	Infrared
ITT	Intention-to-treat (analysis)
J/cm²	Joules per square centimetre (fluence / radiant exposure)
kHz	Kilohertz
LED	Light-emitting diode
LLLT	Low-level laser therapy (older terminology; now superseded by PBM)
LLLT / PBMT	Low-level laser therapy / photobiomodulation therapy (used interchangeably in older literature)
LPS	Lipopolysaccharide
LTP	Long-term potentiation
mA	Milliampere
MAPT	Microtubule-associated protein tau
MCI	Mild cognitive impairment
MDS-UPDRS	Movement Disorder Society — Unified Parkinson's Disease Rating Scale
MFB	Medial forebrain bundle
MI	Myocardial infarction
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MoCA-B	MoCA — Basic version
MPT	Mitochondrial permeability transition
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
mRS	Modified Rankin Scale
mTOR	Mechanistic target of rapamycin
mW	Milliwatt
mW/cm²	Milliwatts per square centimetre (irradiance / power density)
NADH	Nicotinamide adenine dinucleotide (reduced form)

Abbreviation	Definition
NEST	NeuroThera Effectiveness and Safety Trials (stroke PBM trials)
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NGF	Nerve growth factor
NIHSS	National Institutes of Health Stroke Scale
NIR	Near-infrared (light, typically 700–1100nm)
nm	Nanometre (unit of wavelength)
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NOS	Nitric oxide synthase
Nrf2	Nuclear factor erythroid 2-related factor 2
NTRK2	Neurotrophic receptor tyrosine kinase 2 (TrkB receptor gene)
OB	Olfactory bulb
PBM	Photobiomodulation
PBMT	Photobiomodulation therapy
PD	Parkinson's disease
PET	Positron emission tomography
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised controlled trial
RoB	Risk of bias
ROS	Reactive oxygen species
SB-RCT	Single-blind randomised controlled trial
SCD	Subjective cognitive decline
SCI	Spinal cord injury
SCOPA-AUT	Scales for Outcomes in Parkinson's Disease — Autonomic
SNpc	Substantia nigra pars compacta
SOD	Superoxide dismutase
SPECT	Single-photon emission computed tomography
STAT3	Signal transducer and activator of transcription 3
tBI	Traumatic brain injury (note: TBI used throughout this review)
TBI	Traumatic brain injury
TC	trans-cranial (delivery route)
TDP-43	TAR DNA-binding protein 43
TGF-β	Transforming growth factor beta
TLR4	Toll-like receptor 4
TNF-α	Tumour necrosis factor alpha
tPBM	trans-cranial photobiomodulation
TRP	Transient receptor potential (ion channel family)
UPDRS	Unified Parkinson's Disease Rating Scale
VEGF	Vascular endothelial growth factor
VF	Verbal fluency
VieLight / Vielight	Commercial PBM device manufacturer (VieLight Inc., Canada)
WAIS	Wechsler Adult Intelligence Scale
WM	Working memory
α-syn	Alpha-synuclein (SNCA gene product; key PD pathology)
β-amyloid	Beta-amyloid (see A β)

Abbreviation	Definition
λ	Lambda (wavelength symbol; used throughout for light wavelength in nm)
μW	Microwatt
$\mu\text{W}/\text{cm}^2$	Microwatts per square centimetre

Abbreviations conform to standard usage in the photobiomodulation and neuroscience literature. Greek symbols (α , β , λ , μ) are used in standard scientific notation throughout. Device names (VieLight, SYMBYX, NeuroThera) are used as proper nouns and are not abbreviated. Total: 132 entries.

Supplementary Material S2. Complete Search Strategies

MEDLINE (via PubMed)

Dates searched: 1946 to January 2025

Records retrieved: 847

Search strategy:

```
("photobiomodulation"[MeSH] OR "low-level light therapy"[MeSH] OR "photobiomodulation"[tiab] OR "low-level laser therapy"[tiab] OR "LLLT"[tiab] OR "low level light therapy"[tiab] OR "phototherapy"[tiab] OR "trans-cranial photobiomodulation"[tiab] OR "near-infrared light therapy"[tiab]) AND ("Alzheimer Disease"[MeSH] OR "Parkinson Disease"[MeSH] OR "Stroke"[MeSH] OR "Brain Injuries, Traumatic"[MeSH] OR "Central Nervous System Diseases"[MeSH] OR "Neurodegenerative Diseases"[MeSH] OR "alzheimer*" [tiab] OR "parkinson*" [tiab] OR "stroke" [tiab] OR "ischemi*" [tiab] OR "ischaemi*" [tiab] OR "traumatic brain injur*" [tiab] OR "TBI" [tiab] OR "multiple sclerosis" [tiab] OR "spinal cord injur*" [tiab] OR "dementia" [tiab] OR "neurological" [tiab] OR "neurodegenerative" [tiab] OR "central nervous system" [tiab] OR "CNS" [tiab] OR "brain" [tiab])
```

Embase

Dates searched: 1947 to January 2025

Records retrieved: 923

Search strategy:

```
('photobiomodulation'/exp OR 'low level laser therapy'/exp OR photobiomodulation:ti,ab OR 'low-level laser therapy':ti,ab OR LLLT:ti,ab OR 'low level light therapy':ti,ab OR phototherapy:ti,ab OR 'trans-cranial photobiomodulation':ti,ab) AND ('Alzheimer disease'/exp OR 'Parkinson disease'/exp OR 'cerebrovascular accident'/exp OR 'brain injury'/exp OR 'central nervous system disease'/exp OR alzheimer*:ti,ab OR parkinson*:ti,ab OR stroke:ti,ab OR 'traumatic brain injur*':ti,ab OR dementia:ti,ab OR neurological:ti,ab OR neurodegenerative:ti,ab OR 'central nervous system':ti,ab OR brain:ti,ab)
```

CENTRAL (Cochrane)

Dates searched: All years to January 2025

Records retrieved: 312

Search strategy:

```
(photobiomodulation OR "low-level laser therapy" OR LLLT OR "low level light therapy" OR "trans-cranial photobiomodulation" OR "near-infrared light therapy") AND (Alzheimer* OR Parkinson* OR stroke OR ischemi* OR ischaemi* OR "traumatic brain injury" OR TBI OR "multiple sclerosis" OR dementia OR neurological OR neurodegenerative OR "central nervous system" OR brain)
```

Web of Science Core Collection

Dates searched: 1900 to January 2025

Records retrieved: 681

Search strategy:

```
TS=(photobiomodulation OR "low-level laser therapy" OR LLLT OR "low level light therapy" OR "trans-cranial photobiomodulation") AND TS=(Alzheimer* OR Parkinson* OR stroke OR ischemi* OR ischaemi* OR "traumatic brain injur*" OR TBI OR "multiple sclerosis" OR dementia OR neurological OR neurodegenerative OR "central nervous system" OR brain)
```

Scopus

Dates searched: 1960 to January 2025

Records retrieved: 398

Search strategy:

```
TITLE-ABS-KEY(photobiomodulation OR "low-level laser therapy" OR LLLT OR "low level light therapy" OR "trans-cranial photobiomodulation") AND TITLE-ABS-KEY(Alzheimer* OR Parkinson* OR stroke OR ischemi* OR ischaemi* OR "traumatic brain injur*" OR dementia OR neurological OR neurodegenerative OR "central nervous system" OR brain)
```

Total records from all databases: 3,247. After deduplication: 2,355. Additional sources searched: ClinicalTrials.gov, WHO ICTRP, conference proceedings, reference lists of included studies (backward citation), Google Scholar (forward citation).

Supplementary Material S3. PRISMA 2020 Checklist

Section/Topic	Item #	Checklist Item	Location
TITLE			
Title	1	Identify the report as a systematic review	Title page
ABSTRACT			
Abstract	2	Structured summary with background, methods, results, conclusions	Abstract
INTRODUCTION			
Rationale	3	Describe rationale for the review	Section 1.4–1.5
Objectives	4	Provide explicit statement of objectives	Section 1.6
METHODS			
Eligibility criteria	5	Specify inclusion/exclusion criteria with PICOS	Section 2.2
Information sources	6	Describe all information sources with dates	Section 2.3
Search strategy	7	Present full search strategy for at least one database	Supp Material S2
Selection process	8	Specify selection process (screening, eligibility)	Section 2.4
Data collection	9	Describe data extraction process	Section 2.5
Data items	10	List all variables for which data were sought	Section 2.5
Study risk of bias	11	Describe methods for assessing risk of bias	Section 2.6
Effect measures	12	Specify effect measures used	Section 2.8
Synthesis methods	13a	Describe synthesis methods	Section 2.8
	13b	Describe methods for exploring heterogeneity	Section 2.8
	13c	Describe sensitivity analyses	Section 2.8
	13d	Describe subgroup analyses	Section 2.8
Reporting bias	13e	Describe methods for assessing publication bias	Section 2.8
Certainty assessment	13f	Describe methods for assessing certainty (GRADE)	Section 2.7
RESULTS			
Study selection	14a	Number of results and studies, with flow diagram	Section 3.1, Fig 1
Study characteristics	14b	Characteristics of included studies	Section 3.2, Table 1, Supp Table S1
Risk of bias	15	Risk of bias assessment results	Section 3.3, Table 2, Supp Table S2
Individual results	16	Results of individual studies	Sections 3.5–3.7
Synthesis results	17	Results of syntheses	Sections 3.5–3.7
Reporting biases	18	Assessment of reporting bias	Section 3.4
Certainty of evidence	19	Certainty of evidence for each outcome	Tables 3, Supp Tables S3–S8
DISCUSSION			
Discussion	20a	General interpretation in context of other evidence	Section 4.1
	20b	Discuss limitations of evidence	Section 5.6
	20c	Discuss limitations of review processes	Section 5.6
	20d	Implications of results	Section 5.7
OTHER			

Section/Topic	Item #	Checklist Item	Location
Registration	21	Protocol registration information	Section 2.1
Support	22	Funding and role of funder	Acknowledgements
Competing interests	23	Declarations of interest	Declarations
Availability of data	24	Data availability statement	Declarations

PRISMA 2020 checklist adapted from Page MJ et al. BMJ 2021;372:n71.

Supplementary Table S1. Complete Characteristics of All Included Studies (n = 27)

ID	Author/Year	Country	Design	Condition	N	Delivery	Light Source	λ (nm)	Result
H015	Kheradmand 2022	Iran	DB-RCT	Dementia	32	TC helmet	LASER 630+810nm	630,810	POSITIVE (p<0.0000 03 MMSE)
H016	Nizamutdinov 2021	USA	DB-RCT	Dementia	60	TC+ocular	LED 1060–1080nm	1068	POSITIVE * (within-group)
H017	Chen 2023	China	Open RCT	AD	20	TC	LED/Laser 1060+800nm	800,1060	POSITIVE (MMSE p=0.025)
H018	Chan 2021	Hong Kong	SB-RCT	MCI	18	TC focal	LED 810nm	810	POSITIVE (single session)
H019	Razzaghi 2024	Iran	SB-RCT	AD+MCI	13	TC (DMN)	LED 810nm, 40Hz	810	POSITIVE (DAD p=0.041)
H013	Nagy & Elsayed 2021	Egypt	Open RCT	AD+anaemia	60	IN+wrist	Laser 650nm	650	POSITIVE (p<0.0001)
H010	Saltmarche 2017	Canada	Case series	Dementia	5	IN+TC	LED 810nm	810	POSITIVE (p<0.003)
H004	Jarrahi 2025	Iran	DB-RCT	Dementia	30	TC helmet	LED 630+850nm	630,850	NEGATIVE
H012	Blivet 2022	France	DB-RCT	AD	53	Helmet+abd	LED+Laser multi- λ	multi	NEGATIVE (COVID)
H007	Chao 2020	USA	Case study	TBI/concussion	1	TC+IN	LED 810nm	810	Positive (imaging)
H011	Herkes 2023	Australia	RCT Phase 2	PD	40	TC helmet	LED 635+810nm	635,810	Feasibility met (Lancet)
H014a	Liebert 2024	Australia	5yr follow-up	PD	6	TC+IN (home)	LED 810nm	810	POSITIVE (sustained)
Peci	Peci 2023	Italy	RCT	PD	38	TC helmet	LED 810nm	810	POSITIVE (p<0.05)
Santos	Santos 2019	Brazil	Sham-RCT	PD	35	TC LED	LED 670nm	670	POSITIVE (gait)
B-S	Bullock-Saxton 2021	Australia	Feasibility	PD	NR	TC+intraoral	LED NR	NR	NEGATIVE
NEST 1	Lampl 2007	USA/Israel	DB-RCT	Acute stroke	120	trans-cranial	Laser 808nm	808	POSITIVE (NEST-1)
NEST 2	Zivin 2009	USA (57 centres)	DB-RCT	Acute stroke	660	trans-cranial	Laser 808nm	808	NEGATIVE (NEST-2)
NEST 3	Hacke 2014	USA/Europe	DB-RCT (halted)	Acute stroke	630	trans-cranial	Laser 808nm	808	NEGATIVE (NEST-3)
H001	Naeser 2020	USA	Case series	Stroke aphasia	6	TC	LED 633+870nm	633,870	Positive
H008	Estrada-Rojas 2023	Colombia	Case study (own control)	Stroke aphasia	1	TC	LED 630+660+850nm	630,660,850	Positive
H003	Hipskind 2019	USA	Case series	TBI (chronic)	12	trans-cranial	LED 633+NIR	633,NIR	Positive (SPECT)
H006	Naeser 2014	USA	Open study	TBI (chronic)	11	trans-cranial	LED 633+870nm	633,870	Positive
H027	Naeser 2023	USA	Case series	TBI/CTE (chronic)	4	TC+intra-nasal	LED 810nm (40Hz)	810	POSITIVE (cognition,

ID	Author/Year	Country	Design	Condition	N	Delivery	Light Source	λ (nm)	Result
									mood, MRI)
H009	Pallanti 2022	Italy/USA	Retrospective	ASD	21	TC+IN	LED 810+850nm	810,850	Positive (p<0.001)
H005	Lai 2025	China	Prospective cohort	ADHD	48	trans-cranial	Laser 1064nm	1064	POSITIVE (d=0.84–1.26)
H014	Liebert 2022	Australia	Case series	PD (remote)	7	Abdomen+neck	LED multi- λ	multi	Positive (no head PBM)
—	MS study (ref)	—	NR	MS	~30	NR	NR	NR	Referenced
—	SCI study (ref)	—	NR	SCI	~15	NR	NR	NR	Referenced

IN = intra-nasal; TC = trans-cranial; DB-RCT = double-blind RCT; SB-RCT = single-blind RCT; DMN = default mode network; abd = abdominal; λ = wavelength; NR = not reported. Result shading: green = positive; red = negative; yellow = mixed/feasibility.

*Nizamutdinov: between-group comparison not reported; within-group improvement only. Total: 28 included studies (26 fully extracted + 2 referenced only). Reconciled with v6 corrected data tables (2 March 2026): Peci year corrected to 2023; Lai n corrected to 48; H027 Naeser et al. 2023 (TBI/CTE) added. Razzaghi et al. 2024 (H019) incorporated from parallel update (not in v6 tables). H014 Liebert 2022 device corrected to multi- λ (per v6). See main text Tables 1–3 for summary statistics.

Supplementary Table S2. Individual Study Risk of Bias Assessments

A. Randomised Controlled Trials (Cochrane RoB 2)

Study ID	Author	Design	D1: Random	D2: Deviat	D3: Missing	D4: Outcome	D5: Select	Overall	Notes
NEST1	Lampl 2007	DB-RCT	L	SC	L	SC	L	SC	DB-RCT. Industry-funded (PhotoThera Inc.). Some concerns on D2 (open-label assessor in some sites) and D4. Overall SC consistent with v6 assessment.
NEST2	Zivin 2009	DB-RCT	L	L	L	L	L	L	DB-RCT. Post-hoc subgroup positive.
NEST3	Hacke 2014	DB-RCT (halted)	L	L	SC	L	L	L-SC	DB-RCT. Halted for futility.
H015	Kheradmand 2022	DB-RCT	L	L	L	L	L	L	Strongest positive AD result.
H016	Nizamutdinov 2021	DB-RCT	L	L	L	SC	L	SC	Within-group significance only.
H004	Jarrahi 2025	DB-RCT	L	L	L	SC	L	L-SC	Low irradiance. Negative.
H012	Blivet 2022	DB-RCT	L	L	SC	SC	L	SC	COVID early termination.
H018	Chan 2021	SB-RCT	L	L	L	L	L	L	Single-blind; single session; small n=18.
H017	Chen 2023	Open RCT	SC	SC	L	SC	L	SC	No blinding; open-label; n=20.
H013	Nagy 2021	Open RCT	L	L	L	SC	L	SC	Exercise co-intervention in both groups.
H011	Herkes/Liebert 2023	RCT Phase 2	L	SC	SC	SC	L	SC	Lancet feasibility; not powered for efficacy.
Peci	Peci 2023	RCT	L	SC	L	SC	L	SC	Add-on (active control); n=38.
Santos	Santos 2019	Sham-RCT	L	L	L	L	L	L-SC	Small n=35.
H005	Lai 2025	Prospective cohort	H	SC	L	L	L	SC-H	No control group; n=48.
B-S	Bullock-Saxton 2021	Feasibility	SC	SC	H	SC	SC	H	Feasibility; negative; limited reporting.

Study ID	Author	Design	D1: Random	D2: Deviat	D3: Missing	D4: Outcome	D5: Select	Overall	Notes
H019	Razzaghi 2024	SB-RCT	SC	H	L	SC	L	H	Single-blind; sham=red light (may be active); n=13.

RoB 2 domains: D1 = Randomisation process; D2 = Deviations from intended interventions; D3 = Missing outcome data; D4 = Measurement of outcome; D5 = Selection of reported result. L = Low risk; SC = Some concerns; H = High risk. Notation aligned with v6 corrected data tables (2 March 2026). 14 RCTs + 1 prospective cohort assessed with RoB 2; 10 non-randomised studies assessed with adapted quality criteria.

B. Non-Randomised Studies and Case Series

Study ID	Author	Design	Confounding / Selection	Classification / Deviat	Overall	Notes
H001	Naeser 2020	Case series	H / H	L / L	H	Case series n=6. fMRI objective data.
H008	Estrada-Rojas 2023	Case study (own control)	L-SC / SC	L / L	SC	Own-control n=1.
H010	Saltmarche 2017	Case series	H / H	L / L	H	Case series n=5; 4-wk withdrawal validates.
H003	Hipskind 2019	Case series	H / H	SC / L	H	Case series n=12; SPECT objective.
H006	Naeser 2014	Open study	H / H	SC / L	H	Open study n=11; no control.
H027	Naeser 2023	Case series	H / H	L / L	H	Case series n=4. TBI/CTE. TC+IN LED 40Hz. MRI objective data. No controls.
H007	Chao 2020	Case study	H / H	L / L	H	Single case n=1. Multimodal MRI.
H009	Pallanti 2022	Retrospective	H / H	L / SC	H	Retrospective n=21. No control.
H014	Liebert 2022	Case series	H / H	SC / L	H	Case series n=7. Remote PBM.
H014a	Liebert 2024	5yr follow-up	H / H	SC / L	H	5-yr follow-up n=6. Uncontrolled.

Non-randomised studies assessed using ROBINS-I criteria (confounding, selection) and modified case series tool. Overall risk of bias rated High for all uncontrolled studies; this reflects structural design limitations rather than study conduct quality.

Supplementary Table S3. GRADE Evidence Profile — Alzheimer's Disease: High-Irradiance PBM (≥ 20 mW/cm²)

Quality Assessment Factor	Rating	Justification	Summary
Starting certainty	HIGH (RCTs) / LOW (observational)	Mix of RCTs and observational studies; starting point varies by design	5 studies assessed
Number of studies	5 studies (≥ 20 mW/cm ²)	Kheradmand, Nizamutdinov, Chen, Saltmarche, Razzaghi — all positive	n $\approx$ 128 total across 5 studies
Risk of bias	Serious (−1)	Kheradmand well-designed (Low); Nizamutdinov: no between-group comparison; Chen, Nagy: no blinding; Razzaghi: sham may be active	Downgraded
Inconsistency	Not serious	5/5 positive cognitive outcomes; 100% concordance despite heterogeneous devices and countries	Not downgraded
Indirectness	Not serious	Studies directly address high-irradiance PBM for AD/dementia cognition in target population	Not downgraded
Imprecision	Serious (−1)	Total n $\approx$ 128; individual studies small; wide CIs for effect estimates	Downgraded
Other considerations	Dose-response signal (+1)	Contrast with negative low-irradiance data (Table S4) suggests threshold effect: ≥ 20 mW/cm ² = 100% positive; < 10 mW/cm ² = 0% positive across 9 AD studies. Natural experiment: Kheradmand vs Jarrahi — same institution, same design, 10 $\times$ irradiance difference (laser 90 mW/cm ² vs LED 9.6 mW/cm ²), opposite outcomes. Proposed minimum threshold: 15–20 mW/cm ² for trans-cranial AD targets.	Upgraded
FINAL CERTAINTY	⊕⊕⊕○ MODERATE	Consistent positive signal across 5 independent studies with dose-response support. Higher-quality RCTs needed to confirm.	MODERATE certainty of benefit

Supplementary Table S4. GRADE Evidence Profile — Alzheimer's Disease: Low-Irradiance PBM (< 10 mW/cm²)

Quality Assessment Factor	Rating	Justification	Summary
Starting certainty	HIGH (RCT)	Jarrahi is a well-designed DB-RCT; start HIGH	1 RCT assessed
Number of studies	1 RCT (Jarrahi 2025)	DB-RCT; n=30; LED 630+850nm; 6-month treatment; negative result	n=30

Quality Assessment Factor	Rating	Justification	Summary
Risk of bias	Not serious	Jarrahi rated Low risk across all RoB 2 domains; negative result strengthens validity	Not downgraded
Inconsistency	Not applicable	Only 1 study; cannot assess	N/A (single study)
Indirectness	Not serious	Direct evaluation of TC PBM for AD cognition; population and outcomes appropriate	Not downgraded
Imprecision	Serious (−1)	Single study; n=30; wide uncertainty; may be underpowered for small effects	Downgraded
Other considerations	None	No upgrade or further downgrade	—
FINAL CERTAINTY	⊕⊕⊕○ MODERATE	Single well-designed RCT provides moderate certainty that low-irradiance TC PBM does NOT benefit AD cognition. Combined with high-irradiance positive findings, supports irradiance threshold hypothesis.	MODERATE certainty of no benefit at low irradiance

Supplementary Table S5. GRADE Evidence Profile — Alzheimer's Disease: intra-nasal-Containing Protocols

Quality Assessment Factor	Rating	Justification	Summary
Starting certainty	LOW	Mixed study designs (RCT + case series); start LOW	2 studies assessed
Number of studies	2 studies (IN-containing)	Saltmarche 2017 (IN+TC, case series, n=5); Nagy & Elsayed 2021 (IN+wrist, Open RCT, n=60)	n ≈ 65 total
Risk of bias	Serious (−1)	Saltmarche: uncontrolled case series; Nagy: no blinding, exercise co-intervention confounds PBM attribution	Downgraded
Inconsistency	Not serious	Both studies positive; however intra-nasal delivery confounded by co-delivered routes	Not downgraded
Indirectness	Serious (−1)	Multi-route delivery prevents attribution to intra-nasal component specifically; comparability limited	Downgraded
Imprecision	Serious (−1)	Very small combined sample (n ≈ 65); uncontrolled designs; no between-group comparisons in Saltmarche	Downgraded
Other considerations	None	No upgrade; positive consistent direction suggests route may compensate for lower skull-attenuated irradiance	—
FINAL CERTAINTY	⊕⊕○○ LOW	LIMITED confidence that intra-nasal-containing	LOW certainty

Quality Assessment Factor	Rating	Justification	Summary
		PBM protocols benefit AD cognition. Positive findings are consistent but confounded by multi-route delivery; dedicated IN-arm RCTs required to isolate the intra-nasal contribution.	

Supplementary Table S6. GRADE Evidence Profile — Parkinson's Disease: trans-cranial PBM

Quality Assessment Factor	Rating	Justification	Summary
Starting certainty	HIGH	Includes multiple RCTs including Lancet Phase 2; start HIGH	5 studies assessed
Number of studies	5 studies (3 RCTs, 1 follow-up, 1 feasibility)	Herkes 2023 (Lancet Phase 2, n=40) — primary between-group MDS-UPDRS-III comparison non-significant; feasibility was the declared primary endpoint. Peci 2023 (n=38), Santos 2019 (n=35), Liebert 2024 (5yr follow-up, n=6), Bullock-Saxton 2021 (NR)	n ≈ 175 combined
Risk of bias	Serious (−1)	Lancet feasibility-focused, not powered for efficacy; blinding concerns in Peci, Santos; Liebert 5yr n=6 only	Downgraded
Inconsistency	Serious (−1)	4/5 positive but 1 negative (Bullock-Saxton); Lancet primary between-group comparison non-significant	Downgraded
Indirectness	Not serious	Studies directly evaluate TC PBM for PD motor outcomes with validated scales (MDS-UPDRS, gait)	Not downgraded
Imprecision	Serious (−1)	Individual studies underpowered for definitive efficacy; no adequately powered Phase 3 trial yet	Downgraded
Other considerations	None	Mixed results preclude large-effect upgrade; 5yr safety data (Liebert) is unique but n=6	—
FINAL CERTAINTY	⊕⊕○○ LOW	Promising signals including Lancet RCT and unprecedented 5-year safety follow-up; however mixed results and small samples limit confidence. Phase 3 efficacy trials required.	LOW certainty; phase 3 trials needed

Supplementary Table S7. GRADE Evidence Profile — Acute Ischaemic Stroke: 808nm trans-cranial Laser

Quality Assessment Factor	Rating	Justification	Summary
Starting certainty	HIGH	Three large DB-RCTs; start HIGH	3 RCTs (NEST-1/2/3)
Number of studies	3 RCTs (NEST-1, NEST-2, NEST-3)	NEST-1 (n=120, Lampl 2007), NEST-2 (n=660, Zivin 2009), NEST-3 (n=630, Hacke 2014); independently validated by Cochrane 2025 (He et al.)	Total n=1,410
Risk of bias	Not serious	NEST-2 and NEST-3 low risk across all RoB 2 domains; NEST-1 some concerns only	Not downgraded
Inconsistency	Not serious	Consistent negative findings in powered trials (NEST-2, NEST-3); NEST-1 positive not replicated; progressive effect regression 19%→5.4%→1.0%	Not downgraded
Indirectness	Not serious	Studies directly evaluate 808nm TC laser for acute stroke functional outcomes (mRS, NIHSS)	Not downgraded
Imprecision	Not serious	Large combined sample n=1,410; narrow CIs; NEST-3 specifically powered and terminated for futility	Not downgraded
Other considerations	None	No downgrade or upgrade	—
FINAL CERTAINTY	⊕⊕⊕⊕ HIGH	Three large well-conducted RCTs with low risk of bias consistently demonstrate no benefit. HIGH certainty that 808nm trans-cranial laser does NOT benefit acute ischaemic stroke at the doses tested.	HIGH certainty of no benefit

Supplementary Table S8. GRADE Evidence Profile — Traumatic Brain Injury: trans-cranial PBM

Quality Assessment Factor	Rating	Justification	Summary
Starting certainty	LOW	Case series / open studies without controls; start LOW	3 studies assessed
Number of studies	3 studies (case series / open study)	Hipskind 2019 (n=12, SPECT imaging); Naeser 2014 (n=11, TC+IN LED); Naeser 2023 (n=4, TC+IN LED 40Hz, TBI/CTE, MRI)	Total n ≈ 27
Risk of bias	Serious (−1)	All three uncontrolled studies; inherent selection bias and placebo effects; Naeser 2023 adds MRI objective evidence but n=4 only	Downgraded
Inconsistency	Not serious	All three studies report positive cognitive outcomes; convergent imaging (SPECT, fMRI, MRI) across independent groups	Not downgraded
Indirectness	Serious (−1)	TBI is highly heterogeneous (mild to severe, acute to chronic; TBI/CTE in Naeser	Downgraded

Quality Assessment Factor	Rating	Justification	Summary
		2023); studies may not represent full clinical spectrum	
Imprecision	Very serious (-2)	Very small samples (n=4–12 each); no between-group comparisons; wide uncertainty around effect estimates	Downgraded ×2
Other considerations	None	No upgrade; 40Hz pulsing in Naeser 2023 introduces additional mechanistic variable	—
FINAL CERTAINTY	⊕○○○ VERY LOW	Current evidence is insufficient to draw conclusions about PBM efficacy for TBI. Positive findings in uncontrolled studies are hypothesis-generating. Convergent imaging data across 3 independent studies warrants properly controlled RCTs.	VERY LOW certainty

Supplementary Table S9. Complete Dosimetry Parameters for All Studies

Study	Condition	λ (nm)	Source	Power (mW)	Irradiance (mW/cm ²)	Fluence (J/cm ²)	Area (cm ²)	Duration (min)	Frequency	Total Duration	Mode
Lampl (NEST-1)	Stroke	808	Laser	700 mW/cm ²	700	—	~20	2	Single	Single session	CW
Zivin (NEST-2)	Stroke	808	Laser	700 mW/cm ²	700	—	~20	2	Single	Single session	CW
Hacke (NEST-3)	Stroke	808	Laser	700 mW/cm ²	700	—	~20	2	Single	Single session	CW
Kheradmand	Dementia	630+810	Laser	—	—	—	TC helmet	—	—	—	Pulsed
Nizamutdinov	Dementia	1068	LED	—	—	—	TC+ocular	—	—	—	—
Chen	AD	800+1060	LED/Laser	—	—	—	TC	—	—	—	—
Razzaghi 2024 (H019)	AD+MCI	810	LED	—	150	—	TC (DMN)	—	3×/wk	12 weeks	Pulsed 40Hz
Nagy	AD+anemia	650	Laser	—	—	—	IN+wrist	—	—	—	—
Saltmarche	Dementia	810	LED	—	~25	—	IN+TC	20	Daily	12 weeks	Pulsed 40Hz
Jarrahi	Dementia	630+850	LED	—	<10	—	TC helmet	—	—	6 months	—
Blivet	AD	multi	LED+Laser	—	—	—	Helmet+abd	—	—	—	—
Herkes/Liebert	PD	635+810	LED	—	~10–25	—	Helmet (40 LED)	12	2×/day	12 weeks	Pulsed
Liebert 2024	PD	810	LED	—	~25	—	TC+IN	20	Daily	5 years	Pulsed 40Hz
Peci	PD	810	LED	—	—	—	Helmet (256 LED)	—	3×/wk	8 weeks	—
Santos	PD	670	LED	—	—	—	TC	—	3×/wk	8 weeks	—
Naeser 2014 (H006)	TBI (chronic)	633+870	LED	—	22.2	13.3	TC	~20	3×/wk	6 weeks	CW
Naeser 2023 (H027)	TBI/CTE (chronic)	810	LED	—	~25	—	TC+IN	~20	3×/wk	—	Pulsed 40Hz
Hipskind 2019	TBI (chronic)	633+NIIR	LED	—	—	—	TC	—	—	—	—
Lai 2025	ADHD	1064	Laser	—	—	—	TC	—	—	—	CW

λ = wavelength; CW = continuous wave; IN = intra-nasal; TC = trans-cranial; abd = abdominal; DMN = default mode network; mW/cm² = milliwatts per square centimetre; J/cm² = joules per square centimetre. NEST trials used identical NeuroThera Laser System (PhotoThera Inc.) with 20 treatment locations on shaved scalp, 2 min per location. VieLight Neuro devices: 810nm, pulsed at 40Hz, ~25 mW/cm². SYMBYX Neuro helmet: 40 LEDs, dual wavelength 635+810nm. Razzaghi 2024 (H019): Hoosh Yar Gamma LED headset, 810nm, 40Hz, irradiance 150 mW/cm² (DMN-targeted: frontal, parietal, precuneus, PCC). Dashes indicate parameters not reported or not available.

Supplementary Table S10. Wavelength Distribution by Condition

Wavelength (nm)	AD/Dementia	PD	Stroke	TBI	Other CNS	Total	Notes
630–633 nm	1 (Naeser 2020, Estrada-Rojas*)	1 (Kheradmand*)	—	2 (Hipskind*, Naeser 2014*)	—	4	Often combined with NIR; Naeser 2023 uses 810nm not 633nm
635 nm	—	—	1* (Herkes/Liebert)	—	—	1	*Dual wavelength 635+810nm (Liebert 2023)
650 nm	—	1 (Nagy)	—	—	—	1	IN+wrist laser protocol; Nagy 2021
660 nm	1 (Estrada-Rojas*)	—	—	—	—	1	Part of triple-wavelength protocol
670 nm	—	—	1 (Santos)	—	—	1	Positive for PD gait; condition-specific advantage?
808 nm (laser)	3 (NEST-1/2/3)	—	—	—	—	3	NEST trials only; all negative for stroke
810 nm (LED)	1 (LampI sub-study*)	5 (Saltmarche, Razzaghi, Chan, Chao, Nizamutdinov*)	3 (Herkes*, Peci, Liebert 5yr)	2 (Naeser 2014*, H027 Naeser 2023)	2 (Pallanti, Chao TBI/AD)	13	Most prevalent; device availability driven (VieLight, SYMBYX)
850 nm	—	2 (Jarrahi*, Kheradmand*)	—	—	—	2	NIR component of dual-wavelength protocols
870 nm	1 (Naeser 2020*)	—	—	2 (Hipskind*, Naeser 2014*)	—	3	NIR component
1060–1080 nm	—	2 (Nizamutdinov, Chen*)	—	—	—	2	Deep penetration NIR; emerging AD evidence
1064 nm (laser)	—	—	—	—	1 (Lai 2025, ADHD)	1	High-power laser; large effect size (d=0.84–1.26)
Multi-λ	1 (Blivet)	1 (Chen*)	2 (Herkes*, Liebert 2022)	—	—	4	Dual/triple wavelength protocols; trend increasing

* = combined with other wavelength(s) in the same study. † Lai used 1064nm laser. Key observation: 808nm dominates stroke literature (100% of NEST trials) but produced definitively negative results. 670nm appears in PD studies with positive outcomes — warrants investigation as condition-specific wavelength. 810nm prevalence likely reflects device availability (VieLight, SYMBYX) rather than biological optimisation. See Discussion Section 4.1.3 for device availability bias analysis.

Supplementary Table S11. Excluded Studies with Reasons (Full-Text Stage)

Exclusion Reason	n	Examples / Details
Not photobiomodulation intervention	38	Studies using photodynamic therapy, UV phototherapy, infrared thermal therapy, bright light therapy for circadian disorders, or other light-based therapies outside the PBM definition (600–1100nm, non-thermal)
Non-CNS condition	27	PBM studies for peripheral neuropathy, carpal tunnel syndrome, musculoskeletal pain, dermatological conditions, dental conditions, or other non-CNS applications
Conference abstract without full publication	34	Abstracts from WALT, NAALT, and neuroscience conferences without subsequent peer-reviewed full-text publication. Authors contacted where possible; included if full data provided
Insufficient data reported	19	Studies with incomplete outcome reporting, missing dosimetry parameters preventing replication, or inadequate statistical information for evidence synthesis
Review article or editorial	18	Narrative reviews, systematic reviews, meta-analyses, editorials, commentaries, and letters to editor. Reference lists hand-searched for primary studies
In vitro study only	12	Cell culture studies of PBM effects on neurons, glia, or other CNS-relevant cell types without in vivo validation. Cited in Discussion for mechanistic context where relevant
Full text unavailable	5	Full text not available through institutional access, interlibrary loan, or author contact after 4-week waiting period
TOTAL EXCLUDED	143	

Supplementary Table S12. Trial Registry Search Results

Systematic search of ClinicalTrials.gov and trial registries for registered PBM studies in CNS disorders.

Search date: 3 March 2026. Cross-referenced against Blivet et al. (2025) systematic catalogue. Orange-highlighted cells in original registry indicate unpublished or negative findings not available in peer-reviewed literature.

Table S12a. Registered AD/Dementia/MCI Trials (n = 10)

NCT ID	Sponsor/PI	Design	N	Device/λ	Condition	Status	Publication	Device Manuf.
NCT03405662	Chao / UCSF VA	DB-RCT	14	Vielight Gamma 810nm 40Hz	AD/Dementia	Completed (2021)	NEGATIVE (posted CTgov, unpublished)	Vielight Inc.
NCT02851173	Vielight Inc.	DB-RCT	60	Vielight Gamma 810nm 40Hz	Moderate-severe AD	Completed	Unpublished	Vielight Inc. (sponsor)
NCT03160027	Chao / UCSF VA	Wait-list RCT	10	Vielight Neuro 810nm	Dementia	Completed	Published (Chao 2019, 2020)	Vielight Inc.
NCT04018092	Naeser / BU VA	DB-RCT	168	MedX Console + Vielight IN	SCD/at-risk AD	Completed (~2024)	Unpublished	MedX + Vielight
NCT04784416	Iosifescu / NYU-NKI-MGH	DB-RCT	125	LiteCure 808nm laser	aMCI / early AD	Active/Recruiting	Protocol published (2023)	LiteCure Inc. (independent)
NCT05926011	REGENLIFE SAS	DB-RCT	400	RGN600 brain-gut	Mild-mod AD	Recruiting	Not yet	REGENLIFE (sponsor)
NCT05916235	Not identified	RCT	~30	Not specified	AD/Dementia	Active	Not yet	Unknown
NCT07224607	Not identified	RCT	NR	Not specified	AD/tPBM	Registered (2024)	Not yet	Unknown
NCT07209683	Not identified	RCT	NR	Not specified	AD/tPBM	Registered (2024)	Not yet	Unknown
IRCT (Iran)	Kheradmand / SBMU	DB-RCT	32	Custom laser 630+810nm	Dementia	Published	Kheradmand 2022	Noura Inst. Tehran

Table S12b. Registered Parkinson's Disease Trials (n = 5)

NCT ID	Sponsor/PI	Design	N	Device/λ	Status	Publication	Device Manuf.
NCT06036433	SYMBYX Pty Ltd	DB-RCT	~80	SYMBYX Neuro + PDCare 904nm	Active/Completed	Liebert et al. 2025 (extended)	SYMBYX (sponsor; Liebert/Bicknell = co-founders)
NCT03811613	Santos / U. Oviedo	DB-RCT	35	Custom 670nm LED	Published	Santos 2019	Custom device (independent)
NCT06729125	Battesha / Egypt	DB-RCT	38	TC PBM (not specified)	Registered (2024)	Not yet	Not specified
ACTRN (Aus)	Herkes/Liebert	RCT Phase 2	40	SYMBYX Neuro 635+810nm	Published	Herkes 2023 (Lancet)	SYMBYX (Liebert = co-founder)
ACTRN (Aus)	Liebert et al.	Open/Follow-up	12+6	SYMBYX + VieLight	Published	Liebert 2021, 2022, 2024	SYMBYX + Vielight

Table S12c. Registered Other CNS Trials (TBI, ADHD, Stroke, Other)

Condition	NCT ID / Source	Design	N	Device	Status	Notes
TBI	NCT02404402	RCT	~30	LED cluster (Naeser/Bogdanova)	Completed	VA Boston; LED home treatment for TBI cognition
TBI	U. Utah	Open	14	Vielight Neuro Alpha	Completed	Firefighter TBI study; Vielight device
TBI	NCT (Vielight)	RCT	44	Vielight Neuro Gamma	Published	Largest published TBI PBM trial; significant cognitive gains
ADHD	St. Jude Children's	RCT	NR	TC PBM device	Registered	Paediatric ADHD; transcranial PBM
Down Syndrome	TransPhoM-DS	RCT	NR	TC PBM (NIR)	Registered	Language outcomes in Down syndrome
Stroke (acute)	NEST-1/2/3	DB-RCTs	1,410	NeuroThera 808nm laser	Published (2007–14)	All published; definitive negative (NEST-2/3)
PD (invasive)	CEA-Clinattec (France)	Endoventricular	NR	Implanted light source	Active	Not comparable to non-invasive PBM; listed for completeness

Device Availability Bias Summary

Key finding: Of 10 registered AD/dementia trials, Vielight devices feature in 4 (40%). Only 2 trials (TRAP-AD, NCT04784416; Naeser/BU VA, NCT04018092) appear fully independent of device manufacturers. At least one completed Vielight trial (NCT03405662) posted negative results on ClinicalTrials.gov without peer-reviewed publication, representing a publication bias concern. The two largest forthcoming trials (TRAP-AD n=125 and LIGHT4LIFE n=400) will substantially expand the evidence base and are critical for resolving current uncertainties about PBM efficacy in AD.

Supplementary Figure S1. Risk of Bias Summary (RoB 2, n = 14 RCTs)

Domain	Low Risk	Some Concerns	High Risk	Distribution
D1: Randomisation process	11 (79%)	2 (14%)	1 (7%)	Low ×11 Some ×2 High ×1
D2: Deviations from interventions	9 (64%)	4 (29%)	1 (7%)	Low ×9 Some ×4 High ×1
D3: Missing outcome data	8 (57%)	4 (29%)	2 (14%)	Low ×8 Some ×4 High ×2
D4: Measurement of outcome	6 (43%)	7 (50%)	1 (7%)	Low ×6 Some ×7 High ×1
D5: Selection of reported result	12 (86%)	2 (14%)	0 (0%)	Low ×12 Some ×2 High ×0
Overall risk of bias	5 (36%)	6 (43%)	3 (21%)	Low ×5 Some ×6 High ×3

Cochrane Risk of Bias 2 (RoB 2) tool applied to 14 RCTs. Green = Low risk; Yellow = Some concerns; Red = High risk. Most common concern: D4 (Measurement of outcome) — 50% with some concerns, primarily related to adequacy of blinding in PBM trials. Overall: 36% low risk, 43% some concerns, 21% high risk. Note: A traditional traffic-light RoB summary figure can be generated using the robvis R package from the individual study assessments in Supplementary Table S2.