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Improvements in clinical signs and symptoms of Parkinson's disease using photobiomodulation: a five-year follow-up

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Abstract

Background Parkinson's disease is a progressive neurodegenerative disease characterized by clinical motor signs and non-motor symptoms that severely impact quality of life. There is an urgent need for therapies that might slow, halt or even reverse the progression of existing symptoms or delay the onset of new symptoms. Photobiomodulation is a therapy that has shown potential to alleviate some symptoms of Parkinson's disease in animal studies and in small clinical trials.

Objective To assess long-term effectiveness of photobiomodulation therapy in a cohort of Parkinson's disease individuals after five years of continuing therapy.

Methods Eight participants of the initial 12 in a previously published study agreed to be reassessed after five years. Seven of these participants had continued home-based, self-applied photobiomodulation therapy three times per week for five years. One participant had discontinued treatment after one year. Participants were assessed for a range of clinical motor signs, including MDS-UPDRS-III, measures of mobility and balance. Cognition was assessed objectively, and quality of life and sleep quality were assessed using self-reported questionnaires. A Wilcoxon Signed Ranks test was used to evaluate change in outcome measures between baseline (before treatment) and after five years, with the alpha value set to 0.05.

Results Of the seven participants who had continued photobiomodulation therapy, one had a preliminary diagnosis of multisystem atrophy and was excluded from the group analysis. For the remaining six participants, there was a significant improvement in walk speed, stride length, timed up-and-go tests, tests of dynamic balance, and cognition compared to baseline and nonsignificant improvements in all other measures, apart from MDS-UPDRS-III, which was unchanged and one measure of static balance (single leg stance, standing on the unaffected leg with eyes open) which declined. Five of six participants either improved or showed no decline in MDS-UPDRS-III score and most participants showed improvement or no decline in all other outcome measures. No adverse effects of the photobiomodulation therapy were reported.

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Conclusions This study provides a signal that photobiomodulation therapy might safely reduce important clinical motor signs and non-motor symptoms in some Parkinson's disease patients, with improvements maintained over several years. Home-based photobiomodulation therapy has the potential to complement standard therapies to manage symptoms and potentially delay Parkinson's symptom progression.

Trial registration Australian New Zealand Clinical Trials Registry, registration number ACTRN12618000038291p, registered on 12/01/2018.

Keywords Parkinson's disease, Photobiomodulation, Cognition, Motor symptoms, Mobility, Sense of smell

Introduction

Parkinson's disease (PD) is a neurodegenerative disease that is increasing in incidence worldwide, necessitating a focus on disease management as populations age [1]. The motor symptoms of idiopathic PD occur due to the progressive loss of mitochondrial function and death of dopaminergic neurons and the non-motor symptoms as a result of the build-up of a-synuclein [2]. Progression of PD is variable between people with Parkinson's disease (PwP) but typically results in a progressive decrease in mobility, declining balance, and worsening gait, along with a decline in non-motor symptoms such as cognition, sleep quality, and sense of smell, with a corresponding decrease in quality of life.

No pharmacological treatment has yet been able to reverse or retard the clinical progression of PD in large trials [3–6]. Dopamine replacement therapy with L-dopa can improve some motor symptoms but has significant "off" periods, can have debilitating side effects that may interrupt its use, and its effectiveness is reduced over time. In addition there is a long list of non-motor symptoms that are unresponsive to L-dopa [7]. Deep brain stimulation (DBS) can reduce motor symptoms, especially in the "off" periods when L-dopa has lost its effect [8]. There is also increasing evidence that exercise can help with PD symptoms [9].

An alternative to traditional PD therapies is photobiomodulation (PBM), which is a device assisted therapy that uses specific wavelengths of light, either LED or laser [10]. PBM provokes sub-cellular, cellular and tissue responses, resulting in wide-ranging therapeutic effects [11]. Photobiomodulation increases mitochondrial membrane potential and ATP production through stimulation of the mitochondria [11], releases reactive oxygen species (ROS) from Complex IV of the electron transport chain, and regulates downstream cellular signalling via ATP, cAMP, ROS, Ca^{2+} and nitric oxide (NO) to influence gene transcription [11, 12]. PBM therapy has proven to be remarkably safe in its over 50 years of clinical use and experimental study, being both non-invasive and free of deleterious side-effects [13–15].

PBM therapy has been shown to be effective for wound healing, pain reduction, inflammatory disorders, osteoarthritis, tendinopathies and other musculoskeletal conditions [16–19], including for oral mucositis and other cancer treatment side effects, where PBM is now included in the Multinational Association of Supportive Cancer Care (MASCC) mucositis treatment guidelines [20]. In more recent years transcranial PBM therapy has been trialled in a number of neurological and neuropsychiatric disorders [21] such as stroke [22], traumatic brain injury [23], post-traumatic stress disorder [24], depression [25] and Alzheimer's disease [26].

Proof-of-concept clinical studies of PBM therapy for PD have been based on extensive in vivo pre-clinical experiments using rodents and primates [27–29], including when the PBM is delivered to areas remote from the head with the head shielded from the light [30–34]. We have previously reported on the initial (one year) results [35] and the three-year follow-up results [36] of a wait-listed proof-of-concept study using both transcranial PBM and remote (abdominal) PBM to treat the motor and non-motor symptoms of PD. We considered the abdomen as a fitting target for PBM to treat PD, due to the strong microbiome-gut-brain axis link in PD [37], and the previous in vivo studies of abdominal PBM, including in non-human primates [30, 31, 38].

The objective of this study was to assess the effect of PBM therapy on motor signs and non-motor symptoms of Parkinson's disease in a small cohort of participants who had commenced treatment in a proof-of-concept study and had continued treatment for 5 years.

Methods

The study was conducted in Adelaide, Australia. The study received human research ethics approval by the Griffith University Human Research Ethics Committee (2018/16) with an extension until the 24th of April 2024 and was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR - a primary registry in the WHO International Clinical Trial Registry Platform), registration number: ACTRN12618000038291p, registered on 12/01/2018. All participants gave written informed consent prior to taking part and all protocols were conducted in accordance with the ethics approval guidelines. The study design, participant characteristics and treatment regimens are as previously described [35, 36]. After the initial clinical treatment period (12 weeks)

participants underwent self or carer delivered home treatment using the protocols previously described [35, 36]. Individual variations to this treatment are described on a case-by-case basis.

Of the original 12 participants, eight consented to be re-tested after five years. Seven of these had continued PBM therapy with varying degrees of consistency for five years, while one had ceased treatment after one year. All participants were under the care of their own neurologist.

Assessment of outcome measures

Participants were assessed by a certified examiner (Specialist Neurologist, author GeH) using the MDS-UPDRS-III (motor). MDS-UPDRS-III had previously been assessed at baseline (before any treatments) by a neurologist assigned by Parkinson's South Australia. Other assessments were performed at baseline, and after approximately one year, two years, three years, and five years. Participants were assessed for mobility using the tests for timed up-and-go (TUG), TUG manual and TUG cognitive, and the 10 m walk test (10MWT) for walk speed and stride length (Table 1). Fine motor skill was tested using the spiral test and dynamic balance was tested using the 15 s step test with both legs.

Static balance was tested using the single leg stance (SLS) and the tandem stance (TS) tests, with both legs and for eyes open and eyes closed. Participants were categorized as having "good", "fair", "poor" or "extremely poor" balance for each test (see Table 1) and each category was given a numerical value (3, 2, 1, 0 respectively). The values were summed to give a combined static balance (CSB) score (Table 1). The maximum possible score was 24. We considered that a CSB score of equal or greater than 12, equivalent to 30 s for each of the four tests conducted with eyes open, as being a "high functional static balance"; a score that would give the participant a reduced risk of everyday falls. Conversely, a CSB score of six, equivalent to two "good" plus two "fair" balance measures with eyes open, was considered to be a "low functional static balance", with a consequent increased risk of falls and the need for walking aids [39, 40].

The non-motor symptoms that were assessed were cognition, quality of life (QoL), and sleep quality. Cognition was assessed with the Montreal Cognitive Assessment

Table 1 Outcome measures assessed before treatment and after five years of continuous home-based treatment with PBM

Outcome measure	Test	Description
Gait	TUG	Assessors measured the time taken for a participant to stand from a chair, walk 3 m, turn around a marker, return to chair and sit down [41]
	TUG manual	As for TUG except that the participant was carrying a cup of water [41]
	TUG cognitive	As for TUG except that the participant was asked to count backwards from 40 by twos [41].
	10MWT speed	Participants walked a 10 m track. After walking 2 m, assessors measured the time taken to walk a further 6 m [42].
	10MWT stride length	During the 10MWT, assessors also counted the number of strides taken to walk the same 6 m [42]
Dynamic balance	Step test	Participants stood with feet together, 10 cm from a 10 cm high step. Assessors counted the number of times that a participant placed their foot repeatedly on the step in 15 s. Both legs were tested [43].
Fine motor skill	Spiral test	The time taken to draw between the lines of a printed Archimedean spiral. A time penalty of 3 s and 5 s were given for touching a line or crossing a line respectively. The dominant hand was tested [44].
Static balance	TS	The time that a participant could stand with one foot in front of the other (heel to toe) until a step was taken, or the participant used a hand to steady themselves. The assessment was terminated at 30 s. The test was repeated with eyes open and closed and both legs were tested [45].
	SLS	The time that a participant could stand with one foot raised in the air a step was taken, or the participant used a hand to steady themselves. The assessment was terminated at 30 s. The test was repeated with eyes open and closed and both legs were tested [45].
	CSB	Participants were categorised [46] for each test as: • "extremely poor" balance – unable or unwilling to do the assessment. • "poor" balance – holding TS or SLS for less than 10 s, • "fair" balance – holding TS or SLS for between 10 and 29 s. • "good" balance, holding TS or SLS for the full 30 s. These categories were converted to numerical values of 0, 1, 2, and 3 respectively and summed across the 8 tests [47].
Cognition	MoCA	Participants completed the MoCA test version 8.1 (www.mocatest.org), which was scored by an assessor [48].
Quality of Life	PDQ-39	Participants completed the PDQ-39 to assess QoL across 8 domains. Scores for each domain were divided by the highest possible score for that domain and converted to a percentage. Overall score (PDSI) was the sum of dimension scores divided by 8 [49].
Sleep quality	PDSS	Participants completed the PDSS (original version) with 15 items to assess sleep quality [50].

10MWT = 10 m walk test; CSB = combined static balance; MoCA = Montreal cognitive assessment; QoL = quality of life PDQ-39 = Parkinson's disease questionnaire 39; PD Summary Index = PDSI; PDSS = Parkinson's disease sleep assessment; SLS = single leg stance; TS = tandem stance; TUG = timed up-and-go;

(MoCA) with a maximum score of 30. Quality of life was assessed using the Parkinson's disease questionnaire 39 (PDQ-39), which gives a PDQ-39 summary index (PDQSI) of between 0 and 100, with 0 equating to never having difficulty and 100 equating to always having difficulty. Sleep quality was assessed with the Parkinson's disease sleep scale (PDSS), with a higher score (maximum 150) indicative of better sleep quality.

Outcome measures were compared for paired data between baseline and five-year scores using the Wilcoxon Signed Ranks Test with an alpha value of 0.05.

Results

Participants

Participant demographics and details have been described previously [35, 36]. Eight of the original 12 participants were reassessed at five years. Of the four that were not reassessed, one participant had been diagnosed with multisystem atrophy (MSA) during the first year of the study and discontinued treatment, one participant had moved to an aged care facility and discontinued treatment, and two participants had declined the invitation for reassessment. Full results of outcome measures are available as Supplementary Table 1. Of the eight participants who were re-assessed, seven had continued treatment for five years with varying degrees of adherence to the original regimen. One participant (B3) had discontinued treatment after one year and one participant (A4) had a preliminary diagnosis of MSA after two years but elected to continue treatment. No participants reported any adverse events or side-effects related to the PBM treatment and no participant reported any falls during the five-year period.

Group outcomes to PBM therapy

Results of six participants were included in the group outcomes; B3 (discontinued treatment) and A4 (MSA diagnosis) were omitted. MDS-UPDRS-III assessed at baseline and after five years of PBM therapy showed an unchanged median value (Table 2; Fig. 1A). Most median motor outcome measures were improved at five years compared to baseline, with walk speed, stride length and the step tests significantly improved (Table 2; Fig. 1). The only motor outcome that was not improved was SLS on the unaffected leg with eyes open. Cognition as measured by the MoCA was significantly improved after five years of treatment, while QoL was unchanged, and sleep quality was slightly improved (Table 2; Fig. 1).

Individual responses to PBM therapy

Individual outcome responses to PBM therapy are shown in Fig. 2, together with previously published results for one-, two- and three-year assessments [35, 36].

An increase in MDS-UPDRS-III score indicates decreasing mobility. Each MDS-UPDRS-III score is compared to the score that might be expected if a normal trajectory of decline in motor symptoms was followed. The projected trajectory is based on a PD progression of between 1.4 and 8.9 points per year, reported as the range for annual score increases [51]. Participants A5, B1, B2 and B4 responded well to the PBM therapy over five years with no decline in MDS-UPDRS-III, an improvement in the motor symptoms of mobility, gait and balance and improvement of non-motor symptoms of cognition, quality of life score and sleep quality score. Participants A2 and B5 responded less well with fewer improvements. Participants A4 and B3 showed the least response to PBM therapy, although some outcome measures remained improved after five years of therapy. In general, participants initially improved at the one-year assessments after which outcome measures plateaued or slightly declined.

Participant A2

Participant A2 is female, 74 years of age on enrolment in 2018 and was Hoehn & Yahr stage 2. A2 had a restricted assessment at one-year (no motor assessments) and did not attend reassessments at two and three years due to multiple respiratory tract infections. She had developed rheumatoid arthritis during the second year of PBM therapy, accompanied by swelling in her peripheral joints including hands and feet. She had also developed dystonia in her feet due to levodopa medication. She reported that she is inconsistent with her use of the PBM therapy.

MDS-UPDRS-III A2 showed an increased MDS-UPDRS-III score from baseline to five years of 20/132 to 24/132, which is approximately the minimum that would be expected if a normal trajectory of PD progression was followed (Fig. 2A). She was assessed at five years as Hoehn & Yahr stage 3.

Motor assessments Seven of nine outcome measures were improved above baseline, although TUG and TUG manual showed a deterioration. A2 had high functional static balance at baseline (CSB = 14), which remained the same after five years.

Non-motor assessments A2 had an improvement in MoCA score from 26/30 at baseline to 29/30 at one year. When next assessed at five years the score had returned to almost baseline levels (26.7/30). A2 showed a decline in QoL, with an increase in PDQSI from 17.2/100 to 26.5/100, and decline in six of eight domains, the exceptions being cognition and discomfort. A2 also showed a deterioration in sleep quality, with a decline on the PDSS score from 128/150 to 94.5/150.

Table 2 Medians (inter-quartile ranges) of outcome measures, on enrolment (before PBM treatment) and after PBM treatment for five years

	Baseline	5-years	Number of participants with improved or unchanged symptoms
MDS-UPDRS-III	20 (22.0)	20 (8.5)	5 of 6
Mobility tests			
10MWT walk speed (m/s)	1.21 (0.23)	1.51 (0.20)*	6 of 6
10MWT stride length (m)	0.55 (0.10)	0.86 (0.08)*	6 of 6
TUG (s)	7.85 (0.33)	6.35 (0.60)	5 of 6
TUG manual (s)	8.25 (0.93)	6.55 (0.40)	5 of 5
TUG cognitive (s)	9.55 (1.67)	6.50 (1.05)*	6 of 6
Dynamic Balance test			
step test standing on unaffected leg (s)	11.5 (1.0)	16.5 (2.5)*	6 of 6
step test standing on affected leg (s)	11.5 (4.8)	16.0 (3.8)*	6 of 6
Fine Motor Skill tests			
Spiral test - dominant hand (s)	30.9 (8.39)	28.6 (15.63)	4 of 6
Static Balance tests (s)			
TS affected leg behind eyes open (s)	30.0 (0)	30.0 (0)	6 of 6
TS unaffected leg behind eyes open (s)	30 (14.3)	30.0 (18.3)	6 of 6
SLS on affected leg raised eyes open (s)	9.0 (20.3)	16.8 (17.9)	5 of 6
SLS on unaffected leg eyes open (s)	25.5 (20.3)	17.0 (14.7)	4 of 6
TS affected leg behind eyes closed (s)	4.5 (6.5)	15.0 (17.00)	4 of 5
TS unaffected leg behind eyes closed (s)	2.5 (2.5)	30.0 (19.0)	5 of 5
SLS on affected leg eyes closed (s)	2.0 (5.3)	3.0 (0.9)	3 of 5
SLS on unaffected leg eyes closed (s)	2.5 (1.75)	3.6 (1.3)	4 of 4
CSB score	14 (1.5)	16 (5.5)	5 of 6
Cognition test			
MoCA	26.0 (0.8)	29.5 (2.3)*	6 of 6
Quality of Life			
PDQ-39 score (PDSI)	22.0 (14.6)	21.8 (13.4)	4 of 6
Sleep quality			
PDSS score	106.5 (3.8)	112.8 (29.4)	4 of 6
Sense of smell improvement			4 of 6

*= significant improvement in outcome measure at five years compared to before commencement of PBM therapy ($p<0.05$); 10MWT=10 m walk test; TUG=timed up-and- go; TS=tandem stance; SLS=single leg stance; CSB=combined static balance; MoCA=Montreal Cognitive Assessment; PDQ=Parkinson's disease questionnaire; PDSS=Parkinson's disease sleep scale

Participant comments A2 reported that dystonia in her feet and general tiredness were symptoms that had increased over five years, and that she had also developed disabling knee arthritis. Her sense of smell had improved over the treatment period, and she could now smell perfume and cooking.

Participant A5 Participant A5 is male, 67 years of age on enrolment in 2018, and Hoehn &Yahr stage 2. He reported that he had discontinued the abdominal laser therapy after three years on the study but had continued transcranial infrared LED therapy, although not consistently.

MDS-UPDRS-III A5 showed no deterioration (Fig. 2B) in MDS-UPDRS-III after five years of PBM therapy (15/132 at baseline and five years) and was classified as Hoehn &Yahr stage 2 at five years.

Motor assessments All (non-static balance) outcome measures improved after one year of PBM therapy. Thereafter, some outcome measures continued to improve to two years (walk speed, stride length, TUG manual), while others declined. After five years of PBM therapy, all outcome measures remained improved compared to baseline values. A5 showed high functional static balance on enrolment (CSB=14/24), with a decline at two years, but remained improved above baseline (CSB=18/24) after five years of PBM therapy.

Non-motor assessments A5 showed a continual improvement in MoCA score from 27/30 at baseline to 30/30 by three years and dropping slightly to 29.3/30 at five years. He had an improvement in QoL, with a decreased PDQSI score from 30.6/100 to 15.6/100, with improvements in emotional, cognition, communication, and discomfort domains. He had a substantial improvement in sleep quality score from 86/150 to 136/150.

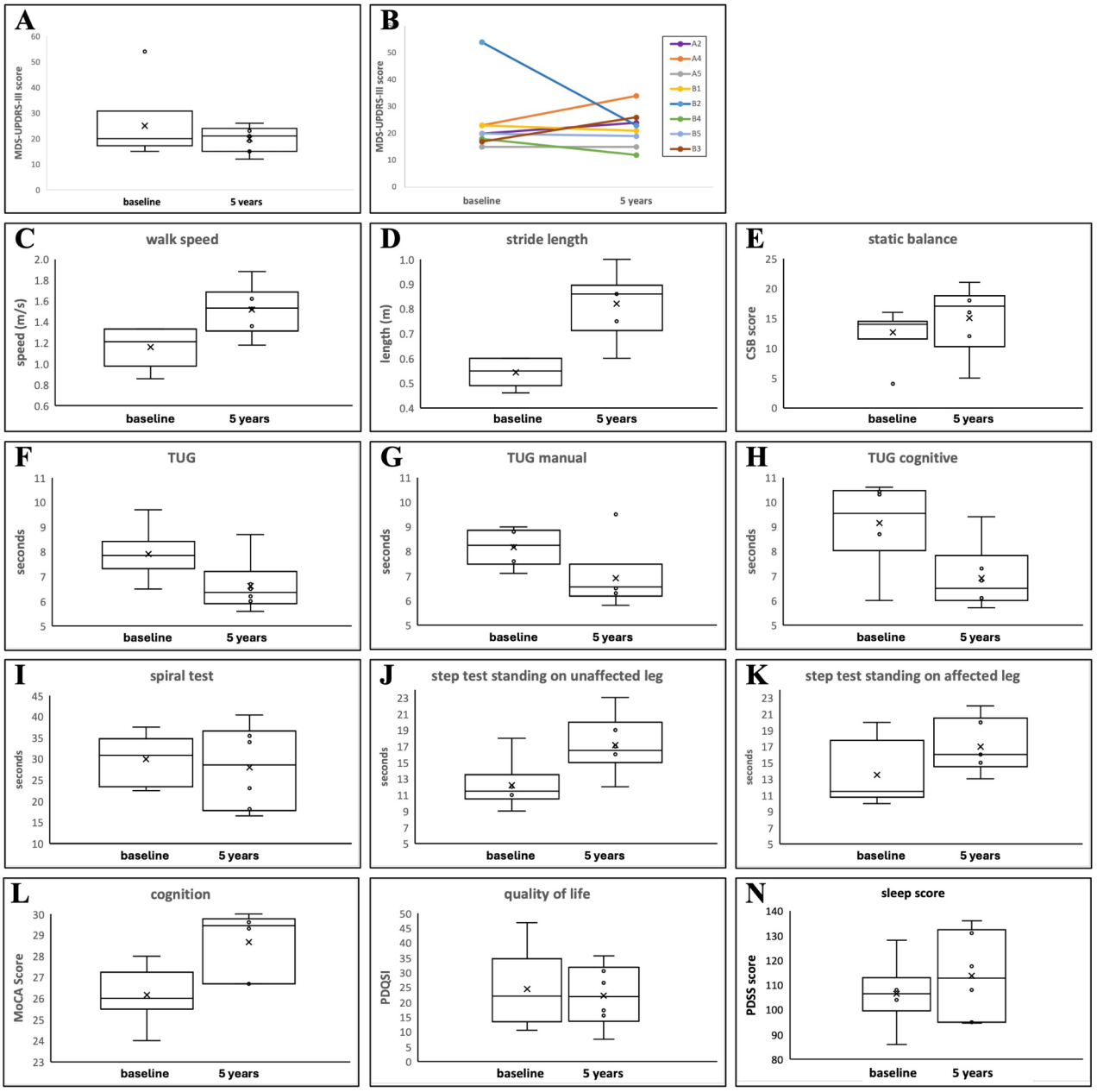

Fig. 1 Changes in outcome measures from one to five years: **A** - grouped MDS-UPDRS-III change; **B** - individual changes in MDS-UPDRS-III; 1 **C** - walk speed over 6 m; **D** - step length over 6 m; **E, C** – static balance score; **F** - timed up-and-go (TUG) test; **G** - TUG manual test; **H** - TUG cognitive test; **I** - spiral drawing test; **J** - step test standing on affected leg; **K** - step test standing on unaffected leg; **L** - Montreal cognitive assessment (MoCA); **M** - Parkinson's disease questionnaire summary index (PDQSI); **N** - Parkinson's disease sleep scale (PDSS)

Participant comments Prior to light therapy A5 reported that he had very interrupted sleep. He reported sleeping for up to eight uninterrupted hours during the first year of PBM therapy. A5 reported that his sense of smell has remained unchanged over the five years of PBM therapy as has his perception of his symptoms. His neurologist has commented on the "mildness of PD symptoms".

Participant B1

Participant B1 is female, 53 years of age on enrolment in 2018 and was Hoehn & Yahr stage 2. She was characterised as young onset Parkinson's disease. B1 reported that she uses her PBM devices relatively consistently three times per week for abdominal treatment and daily for transcranial treatment. During the five-year assessment she was coming to the end of her "on" period and her

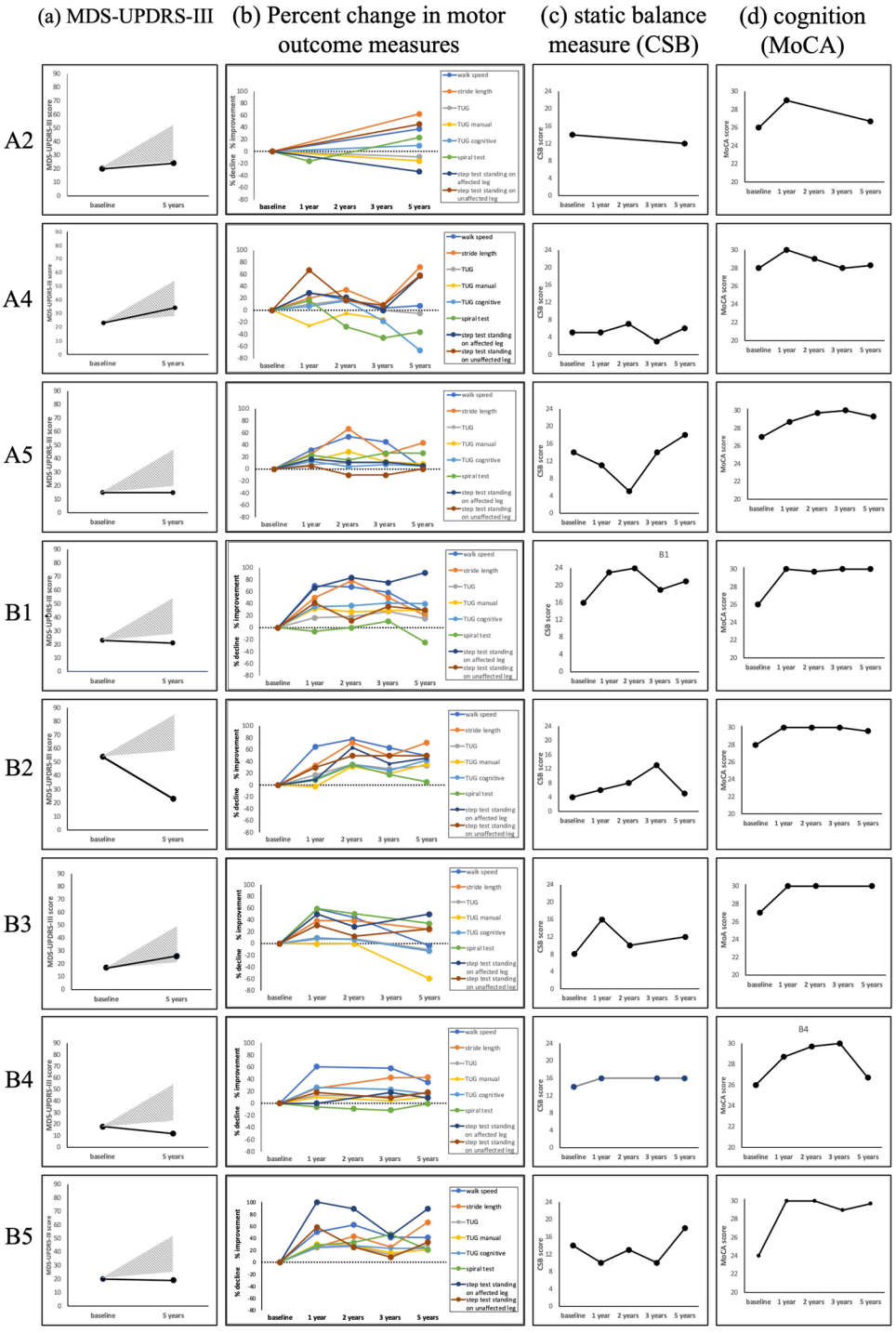

Fig. 2 Individual participant changes in outcome measures over five years for MDS-UPDRS-III, percentage change in motor symptoms from baseline, combined static balance (CSB) score and cognition (Montreal Cognitive Assessment – MoCA). The shaded area in the MDS-UPDRS graph is the score if a normal PD trajectory were to be followed

tremor was visibly increasing, which may have influenced outcome measures.

MDS-UPDRS-III B1 showed a slight increase in her MDS-UPDRS-III score after five years from 21/132 to 23/132 (Fig. 2C) and was assessed as Hoehn & Yahr stage 2 at the five-year reassessment.

Motor assessments B1 showed considerable improvement in outcome measures by one-year, and these have

been substantially maintained for five years. All outcome measures except for the spiral test drawing test remained above baseline after five years of PBM therapy. B1 entered the trial with high functional static balance (CSB=14/24), which improved further over one and two years and remained above baseline (CSB=21/24) after five years of PBM therapy.

Non-motor assessments B1 showed an improvement in MoCA score from 26/30 at baseline to 30/30 at year one and year five. She also showed improvement in QoL with a decreased PDQSI score from 46.7/100 to 30.4/100, and improvements in seven of the eight domains, the exception being discomfort. She had an improvement in sleep quality with her PDSS score improving from 87/150 to 108/150.

Participant comments B1 reported that her sense of smell had slightly improved over the five years of PBM therapy, and that she can now smell perfume. She had noticed motor improvements during the first two years of PBM therapy (improved balance, reduced dystonia and rigidity), but these seem to have diminished since, possibly due to the aftermath of COVID and increasing levodopa, which has resulted in increased dyskinesia. She attributes the "reduced downward trajectory of my symptoms" to the PBM therapy. Her neurologist and other health professionals have all commented on how well she is doing.

Participant B2

Participant B2 is female, 72 years of age on enrolment in 2018 and was Hoehn & Yahr stage 3. B2 reported that she uses both abdominal and transcranial PBM devices consistently, three times per week.

MDS-UPDRS-III B2 showed a marked reduction (improvement) in MDS-UPDRS-III score from 54/132 to 23/132 (Fig. 2D) and was assessed as Hoehn & Yahr stage 3 on reassessment at five years.

Motor Assessments B2 showed improvement in all outcome measures to one and two years and thereafter the improvements were largely maintained. All outcome measures after five years of PBM therapy were above her initial baseline values. B2 had moderate functional static balance on enrolment (CSB=8/24), which improved at one, two and three years, but then declined at five years (CSB=5/24).

Non-motor Assessments B2 showed an improvement in MoCA score from 28/30 at baseline to 30/30 by one year and this was maintained to five years. She showed an improvement in QoL with a decreased PDQSI score from 26.9/100 to 17.2/100, with improvements in mobility, activities of daily living, stigma, and communication domains. She had an improvement in sleep quality with a PDSS score improving from 105/150 to 117.5/150.

Participant comments B2 reported that her sense of smell had returned from a profound loss (complete anosmia) after 12 weeks of PBM therapy and had continued to improve to three years. B2 has felt better than she expected after five years and is in complete remission from her constipation/diarrhea that she had suffered for many years prior to PBM therapy. Her neurologist is "happy with her progress".

Participant B4

Participant B4 is male, 69 years of age at enrolment in 2018 and was Hoehn & Yahr stage 1. He reported that he used the transcranial PBM device consistently three times per week but has not used the abdominal laser for some months prior to the five-year assessment.

MDS-UPDRS-III B4 showed a reduction in his MDS-UPDRS-III score after five years from 18/132 to 12/132 (Fig. 2E) and was assessed as Hoehn & Yahr stage 2 at five years.

Motor assessments Most outcome measures had improved after one year of PBM therapy and thereafter remained stable and remained improved above baseline measures at the five-year reassessment. B4 entered the study with high functional static balance (CSB=14/24), which has slightly improved and has been maintained over the five years of PBM therapy (CSB=16/24).

Non-motor assessments B4 showed a continual improvement in MoCA score from 26/30 at baseline to 30/30 by year three, decreasing to 26.7/30 at year five. He had an initially high QoL score at baseline (PDQSI=10.5/100), which further improved at five years (PDQSI=7.6/100), with improvements in mobility, emotional, stigma and communication domains but a decline in the discomfort score. He had an improvement in sleep quality score from 108/150 to 131/150.

Participant comments B4 reported that his sense of smell had improved during the five years of PBM therapy and felt that the progression of his PD symptoms had slowed, although he felt that his balance was worse. He is suffering more back pain than five years previously. His neurologist has said that he is "generally very happy with my PD status".

Participant B5

Participant B5 is female, 61 years of age on enrolment in 2018 and was Hoehn & Yahr stage 2. She reported that

she uses both abdominal and transcranial PBM devices consistently every second day.

MDS-UPDRS-III B5 showed a slight reduction in the MDS-UPDRS-III score after five years from 20/132 to 19/132 (Fig. 2F) and was assessed as Hoehn & Yahr stage 2.

Motor assessments B5 showed improvements in all outcome measures at one year but with some outcome measures deteriorating at three years but improving to five years. All outcome measures at five years were improved above baseline. Her functional static balance was high on enrolment (CSB=14/24) and has been maintained for three years and improved at five years (CSB=18/24).

Non-motor assessments B5 showed an improvement in MoCA score from 24/30 at baseline to 30/30 by one year and this was maintained to year five (29.7/30). B5 showed a deterioration in QoL over five years with an increase in PDQSI score from 14.4/100 to 35.7/100, with declines in all domains except for social. Her sleep quality score also declined from 104/150 to 98/150.

Participant comments B5 felt that the PBM therapy gave an initial immediate improvement to her movement and stress but has less effect now. She believes that her balance and mobility have improved with the therapy. She believes that her sense of smell has been lost over time. Her neurologist is "very happy with (her) stage of PD …… and doing well".

Participant A4

Participant A4 is male, 75 years of age at enrolment in 2018 and Hoehn &Yahr stage 2. A4 had a preliminary diagnosis of MSA during the 3rd year of the study.

MDS-UPDRS-III

A4 showed an increased MDS-UPDRS-III score from 23/132 to 34/132, which is in the lower part of expected trajectory for PD (Fig. 2G). He was categorized as Hoehn & Yahr stage 3 at the five-year assessment.

Motor assessments A4 showed improvement in most outcome measures at one year and thereafter a great deal of variation. Four of eight outcome measures were above baseline at five years. He had low functional static balance on enrolment (CSB=5/24) that had improved, although was still low by one year (CSB=9/24). Thereafter his balance has fluctuated but was no worse at five years (CSB=6/24) than at baseline, although he did not feel confident to attempt the TS assessment with eyes closed.

Non-motor assessments A2 had an improvement in MoCA score from 28/30 at baseline to 30/30 at year one. This score then declined at two years and three years to be marginally above baseline (28.3/30) at year five. A4 showed a deterioration in QoL with his PDQSI score increasing from 27.8/100 to 44.1/100, with deterioration in six of the eight domains; the exceptions being communication and discomfort. A4 showed an improvement in sleep quality score from 86/150 to 93/150.

Participant comments A4 had noticed a deterioration in symptoms in the last few months, particularly balance. He believes that his sense of smell has diminished over the five years of the study.

Participant B3

Participant B3 is female and 57 years of age at enrolment in 2018 and was Hoehn & Yahr stage 2. She underwent chemotherapy treatment during the first year of the study and continued PBM therapy for her PD, but this was discontinued after one year. She agreed to be reassessed at two years and five years.

MDS-UPDRS-II

B3 showed an increased MDS-UPDRS-III score from 17/132 to 26/132, which is in the lower range of the expected trajectory for PD (Fig. 2H). She was assessed as Hoehn & Yahr stage 2 at the five-year assessment.

Motor assessments B3 showed improvement in most outcome measures at one year. Thereafter these outcome measures showed deterioration although five of nine outcome measures remained above baseline at five years. She had low functional static balance on entry to the study (CSB=8/24), which improved with PBM therapy at the one-year assessment (CSB=16/24) and declined at five years although was still above baseline (CSB=12/24).

Non-motor assessments B3 showed an increase in MoCA score from 27/30 at baseline to 30/30 by year one, which was maintained to year five. B3 showed a slight improvement in QoL with her PDQSI score decreasing from 36.0/100 to 33.4/100, with a decline in mobility, emotion and social domains, and an improvement in activities of daily living, cognition, and communication domains. B3 showed a slight improvement in PDSS score from 92/150 to 95/150.

Discussion

At this time there are no medications with evidence from Phase 3 trials, that can slow the neurodegeneration that accompanies PD [3–6, 52]. Thus, there is an urgent need for PD therapies that might slow, halt or even reverse the relentless progression of PD symptoms. Such therapies

could help to avoid or at least delay the onset of the more advanced and disabling symptoms of the disease, such as dementia, speech difficulties, and loss of mobility.

In previous studies [35, 36] we have shown that PBM therapy applied as LED transcranially and laser to the abdomen and neck can improve some of the clinical signs and symptoms of Parkinson's disease for up to three years. This current study follows some of the original participants and demonstrates maintenance of initial improvements for five years. Overall, PBM therapy resulted in improvement and stabilisation of clinical signs, symptoms, and health status of PwP over an extended period, including MDS-UPDRS-III, objective motor and non-motor symptoms. PBM, including transcranial PBM, has an excellent safety profile [53–56]. None of the participants in our study has reported any adverse events or side-effects related to the long-term PBM treatment.

Of the six participants who had continued self-applied home-based PBM therapy and who did not have a secondary diagnosis (MSA) during the study, five (A5, B1, B2, B4, B5) responded to the therapy in such a way as to reverse many of their PD symptoms and maintain these improvements for five years. Four of these participants also showed improvements in the subjective measures of QoL and sleep quality. Importantly, there were very few outcome measures that showed deterioration after five years compared to baseline. These improvements and lack of deterioration are important, since a decline in the clinical symptoms of PD would normally be expected over a five-year period. The sixth participant had not attended reassessments at two and three years due to COVID, a series of respiratory infections and rheumatoid arthritis, was less consistent in her use of the PBM therapy and her response to the PBM therapy was more equivocal. Her Hoehn and Yahr staging increased from 2 to 3 over 5 years.

The symptoms of the parkinsonian subtype of MSA may mimic PD and between 30% and 65% of people with MSA may have a response to levodopa, although this tends to be poor and/or short-term [57]. Individuals with MSA tend to decline more rapidly and have a greater number of symptoms that are less common in PD, such as cardiovascular symptoms, dizziness, double vision and seizures [58]. Perhaps surprisingly, A4 with a preliminary diagnosis of MSA, none-the-less improved in several motor assessments including walking speed, stride length, and dynamic balance at one year. Despite the deterioration in most outcome measures after the first year of PBM therapy, a number of outcome measures remained above baseline values at five years. Moreover, static balance, while poor, also did not appear to have deteriorated further in five years. The increase in A4's MDS-UPDRS-III score at five years was at the lower end of the expected increase for someone with PD.

Participant B3, who had not used PBM therapy for over three years, maintained the improvement in a number of motor measures (stride length, dynamic balance, spiral test) and her static balance had not deteriorated below baseline at five years. Her MDS-UPDRS-III score was at the lower end of the increase that would be expected after 5 years.

The placebo effect is acknowledged in clinical trials and is especially prominent in PD clinical trials due to the increased release of dopamine that is elicited due to participation in a study [59, 60]. Both the placebo effect and the Hawthorn effect have been shown to be important factors in studies of PBM therapy for PD [35, 56, 61, 62]. These effects, however, are sustained for a relatively short period [63, 64] and would be expected to be long extinguished after five years of home-based PBM therapy.

There are a number of potential interventions that might give improvements in motor and non-motor symptoms of PD, including the repurposing of currently approved medications such as anti-diabetic agents (such as glucagon-like peptide 1 (GLP-1) receptor agonists) [52] and anti a-synuclein agents (such as prasinezumab) [65]. Establishment of efficacy and safety profiles for pharmaceuticals necessitates long lead-in times before market availability is achieved and medications often carry side effects. While DBS can help many motor symptoms in the "off" period [8], it has less effect over time during the "on" period [66]. Deep brain stimulation may also adversely affect cognition [67] and also carries the usual risks and side-effects of surgery.

Physical exercise is receiving increasing attention as a therapy to improve PD symptoms and potentially delay symptom progression [9]. Participants in our study engaged in regular exercise programs. Retrospective studies suggest that regular exercise is associated with slower motor deterioration and improved QoL [68]. In a small pilot study using the PD Warrior 10-week Challenge exercise program, 17 participants showed significant short-term improvements from baseline in MDS-UPDRS-III, six metre walk test and the PDQ-39 emotional domain [69]. Compliance with exercise by PwP has been shown to be affected by fatigue and motivational factors [70], and a sufficient dose of exercise is required for beneficial effects to be achieved [71]. We speculate that the adjunctive use of PBM therapy could address some of the adherence-related factors that may reduce the efficacy of exercise, paving the way for PwP to comply and continue with exercise and physical activity over the longer term. PBM is known to improve exercise performance and to reduce pain that may be a barrier to exercise [72, 73]. The combined use of PBM and exercise for PD treatment remains to be investigated.

The MDS-UPDRS (motor) assessment is the gold standard to assess motor impairment in PD and is the most widely used assessment tool in clinical research [74]. While MDS-UPDRS shows good reliability and validity, studies that have used the assessment to track PD progression have reported wide variation in the yearly increase in scores (e.g., 1.2 per year [75]; 0.70–1.39 per year [76]; 0.6–3.2 per year [77]; 3.1–3.8 per year [78]; 1.8 per year in a four year study [79]; 11.6 per year [80]). This variation can depend on whether the assessment is done during "on" or "off" periods [80–82], the age of onset of the disease [76, 78], the subtype of the disease, fast versus slow progression [77, 83, 84], the use of oral levodopa vs. levodopa-carbidopa intestinal gel vs. DBS [82] or de novo PD [51]. The common theme, however, is the deterioration of motor symptoms (an increase in MDS-UPDRS-III score) over time. In this study we have demonstrated that PBM therapy in some PwP is able to halt the progressive deterioration in MDS-UPDRS-III scores or even improve scores over an extended period. Five of eight participants showed no deterioration in MDS-UPDRS-III after five years of PBM therapy. The deterioration in the MDS-UPDRS-III score in the remaining three participants was at the lower end of what would be considered a normal PD trajectory. It has been estimated that a decrease of 3.25 points in the MDS-UPDRS-III detects a minimal clinically important difference (MCID) improvement, and an increase of 4.63 points represents MCID worsening [85]. Two participants (B2, B4) satisfied the criterion for an MCID improvement and two participants (A4, B3) the criterion for worsening. It is important to remember that these estimates of MCID are based on six monthly changes in MDS-UPDRS-III, rather than the five-year period in our study.

Falls risk is related to gait impairment, loss of balance, cognitive state, and previous falls history [86]. An estimated 60% of PwP experience at least one fall in the course of their disease with 39% having recurrent falls [87]. The 10MWT and TUG tests have been validated for PD [42, 88], and show a good relationship to mobility, falls risk and PD progression [89]. Improvements in these tests of motor ability, as well as maintenance of balance would mitigate falls risk, thus improving QoL, reducing the risk of serious injury and the loss of confidence that results from falls.

A change in gait is a cardinal feature of PD and gait invariably deteriorates with PD progression, affecting mobility and quality of life, as well as increasing the risk of falls. Levodopa can initially increase walking speed [90] but even with medication, walk speed and other aspects of gait deteriorate with time [91, 92]. One small study showed a 0.15 m/s decrease in walk speed over a two year period [93]. Over longer timeframes (6 years), it has been calculated that walking speed declines by 0.01 m/s per year and step length by 0.009 m per year [94], unrelated to dopaminergic medication and exacerbated by age related changes. A clinically significant walking speed decline has been variously estimated as between 0.11 m/s and 0.25 m/s [95] and between 0.05 m/s and 0.22 m/s [96]. In our study, eight of eight participants were assessed at five years with a longer stride and seven of eight participants with a faster walk speed than at baseline, the exception being B3 who had discontinued PBM therapy after one year.

The TUG test assesses functional mobility and has been validated for PD [42, 88]. It is correlated with and is suggested to predict falls risk in PwP [97–99]. The time taken to complete the TUG test increases with PD progression and might be sufficiently sensitive to track subtle PD motor changes [95]. The minimal detectable change in TUG (the smallest change that can be considered a "true change") has been calculated to be 3.5 s [100]. After five years of PBM therapy, five of six participants in our study showed a reduced time to complete the TUG but none of these reached the 3.5 s threshold. When a second task is added to the TUG (TUG manual, TUG cognitive) gait difficulties are exacerbated and the time taken to complete the TUG is usually increased with increased gait variability [101]. TUG cognitive is also correlated with cognitive ability (MoCA scores) [102]. As with the standard TUG, five of six participants improved with TUG manual and six of six participants improved TUG cognitive in our study.

Balance deteriorates as PD progresses, especially in middle stages of PD and can be useful as a predictor of falls risk [103]. In our study, dynamic balance was tested using a 15 s step test [104] and static balance using the TS and the SLS tests, which are the most discriminatory in the Bergs balance scale [105]. The tests were completed with eyes open and eyes closed to give greater range of scores for each participant in order to capture small changes in the static balance of participants who could complete 30 s of the TS and SLS tests with eyes open (such as B1, B4, B5). Static balance tests with eyes closed will test the proprioception contribution to balance, while with eyes open will test the combination of vision, vestibular and proprioception to balance. In the real-world, static balance with eyes open may be a more relevant measurement to assess falls risk. In our study TS and SLS times were converted to scores and summed to give a CSB score, with a maximum of 24, in order to assess the contribution of static balance to falls risk. We considered that a CSB score of 12 (equivalent to full scores for tests with eyes open) corresponded to a high functional balance that would reduce day-to-day falls risk. Since a decrease in balance is normal with increasing age it is useful to compare the values in our study to normative values in the healthy population. The mean

seconds to failure for TS with eyes closed is 18.3, 13.2 and 9.1 for healthy females and 19.7, 15.4 and 9.0 for healthy males in their 60s, 70s and 80s respectively [106]. For SLS, mean seconds to failure with eyes closed is 3.6, 3.7, and 2.1 for healthy females and 5.1, 2.6 and 1.8 for healthy males in their 60s, 70s and 80s respectively [107]. All participants in our study were worse than the healthy normative values for TS and SLS at baseline, apart from B1 (53 years old at baseline) who was above the normative value for women in their 60s for SLS on her unaffected leg (4.9 s). By the five-year assessment four participants had improved to the extent that they were better than the healthy population in some balance measures. B1 was above normative values for all four TS and SLS tests, A5 and B5 were above normative values for three tests, and A2 was above normative values for one test.

Cognitive impairment is a common and important non-motor symptom in PD, with up to 40% of PwP showing mild cognitive impairment (MCI) [108, 109], and up to 80% going on to Parkinson's disease dementia (PDD) [110] with disease progression and aging. Cognitive impairment is particularly debilitating for PwP, putting additional strain on care givers, and has potentially more effect on quality of life than motor symptoms [111]. Cognitive impairment in PD would be expected to increase over a five-year period. For example, one study of 133 newly diagnosed PwP found that 15% had developed PDD by five years [112]. In a study with 129 participants, the mean annual decline of the Mini-Mental State Exam (MMSE) was found to be 1.1 points per year over four and eight years [113] while a study with 1741 PD participants using the SCales for Outcomes in PArkinson's disease-COGnition (SCOPA-Cog) test (with a maximum score of 43) showed a mean annual decline of 1.9 points over five years [111]. The mean decline in MoCA score has been estimated as between 0.1 and 1.7 points per year in PwP without cognitive impairment and between 2.6 and 3.7 in PD patients with MCI [114]. Even in otherwise healthy individuals, MoCA scores have shown a 0.17 annual decrease over time with aging [115]. In our study, while only one participant could be categorised as having MCI (B5), three others had a score of 26 at baseline, the cut-off for MCI. All participants had an increased MoCA score at one year, including B5 whose score increased to 30. Most participants (6 of 8) maintained their one-year MoCA score for five years, and all participants had a higher MoCA score at five years than at baseline.

The PDQ-39 score is often used in PD studies, but has not always been found to be a reliable measure of PD progression [116]. Changes in PDQSI over time corresponding to worsening QoL has been found to be linear [117], with a mean increase of 1.6 points in 14 months. An MCID for a decline in QoL has been estimated to be a 4.22 point increase, while an MCID for improvement has been estimated to be a 4.72 point decrease [118]. Three participants in our study (A5, B1, B2) showed a decrease in PDQSI beyond that required for an improved MCID. Interestingly, B5, who had responded well to PBM therapy in objective measures of mobility and cognition, showed a decline in QoL (increased PDQSI), including in mobility and cognition domains, indicating that she felt she had not improved despite her objective measures of improvement in both motor signs and cognition. This result reinforces the need for a comprehensive suite of measures in research related to PBM and PD.

The same participants who demonstrated improvement in QoL also showed an improvement in sleep quality, as shown by an increase in the PDSS score. A change in PDSS score of more than 20 points has been considered as a clinically significant change [119] and two participants met this criterion (A5, B4). One participant (A2) showed a clinically significant decline in PDSS score, which her known co-morbidities may have been contributed to.

Loss of sense of smell is common in PwP and may be one of the earliest symptoms of PD, being present in the prodromal period and having the potential to be an early biomarker of PD and to predict disease severity and progression [120, 121]. Olfactory dysfunction may also be related to cognitive decline [122]. Loss of sense of smell does not respond to levodopa or symptomatic medications [123], although olfactory training has been shown to improve olfactory sensitivity. In our study, four of the seven participants (A2, B1, B2, B4) who continued with the PBM therapy reported that their sense of smell had improved and one that their sense of smell had not diminished (A5). One of these participants (B2) reported that her sense of smell had returned from total anosmia that had continued for many years and that her sense of smell had continued to improve over the years of the PBM therapy. While no objective measure of sense of smell was undertaken in this study, the accounts of improvement given by the participants support a number of reports in the literature of olfactory improvement using PBM, including the use of abdominal PBM therapy for PD [124] with sense of smell tested using the University of Pennsylvania Smell Identification Test (UPSIT); the improvement of sense of smell in three of seven participants in a case series using abdominal PBM [125]; the use of transcranial and intranasal treatment in an Alzheimer's disease case study [126]; and the use of transcranial PBM therapy for one case study of a person with Parkinson's disease [127]. In a recent randomised placebo-controlled study using a transcranial helmet [56], sense of smell was regained or improved in 8/33 participants on active treatment while none on sham treatment showed an improvement (unpublished). When treatment was halted 3/4 participants showed a reversal of the

improvement. PBM has also been shown to improve the temporary olfactory dysfunction that can occur during COVID-19 [128].

In addition to the improvements in measures of motor signs, balance, and MoCA, most participants had improvements in the subjective reporting of their PD symptoms as well as a positive reflection of their experience with PBM therapy. Seven of the eight participants who agreed to be re-assessed after five years had continued using the PBM devices on the head and/or abdomen three times per week with varying degrees of consistency for five years. The continuance of self-applied therapy supports our contention that the participants considered the therapy to be of benefit.

The major limitation for this study is the small number that were able to be followed up for reassessment over five years. The five-year study coincided with the SARS-COV-2 pandemic and associated lock downs and restrictions. In addition, the study lacked blinding for both participants and assessors with no control group, which could potentially introduce bias. However, the study's primary strength is the opportunity to assess participants over an extended period of PBM therapy and compare symptoms to the expected trajectory of progression in PD. Furthermore, the study employed both objective assessments of participants' clinical signs as well as subjective assessments, including participants qualitative accounts of their own clinically relevant symptoms.

Conclusion

While the number of participants in this study was small, there is a signal that PBM might improve motor signs and non-motor symptoms in PwP, including balance, mobility, cognition, QoL, sleep quality, and sense of smell, with these improvements being maintained over an extended period. This result is contrary to the normal trajectory of PD symptoms. The long-term maintenance of improvement is clinically meaningful to the participants and well beyond any placebo effect. To our knowledge this is the first study to demonstrate an amelioration of PD symptoms to this degree over an extended period. Importantly, there were no safety concerns, or any adverse side-effects reported.

The positive effect of PBM therapy on various motor signs and non-motor symptoms of PD suggest that a larger, long-term clinical trial investigating this therapy is warranted. Moreover, the synergistic effects of combining PBM therapy with exercise regimens deserves exploration in future studies. If these studies yield successful outcomes, the incorporation of PBM therapy into standard treatment guidelines for PD would be a logical step. The potential benefit of this non-invasive, low-risk home-based therapy, used as an adjunct to established and newer PD therapies, is a substantial improvement in the quality of life for individuals living with this debilitating and intractable neurodegenerative disorder.

Abbreviations

10MWT	10 m Walk Test
ANZCTR	Australian New Zealand Clinical Trials registry
ATP	Adenosine Triphosphate
cAMP	Cyclic Adenosine Monophosphate
CSB	Combined Static Balance
COVID	Coronavirus Disease of 2019
DBS	Deep Brain Stimulation
GLP-1	Glucagon-Like Peptide 1
LED	Light Emitting Diode
MCI	Mild Cognitive Impairment
MCID	Minimal Clinically Important Difference
MDS-UPDRS	Movement Disorder Society Unified Parkinson's Disease Rating Scale
MoCA	Montreal cognitive assessment
MSA	Multisystem Atrophy
NO	Nitric Oxide
PBM	Photobiomodulation
PD	Parkinson's Disease
PDD	Parkinson's Disease Dementia
PDQ-39	Parkinson's Disease Questionnaire 39
PDQSI	Parkinson's Disease Questionnaire Summary Index
PDSS	Parkinson's Disease Sleep Scale
PwP	people with Parkinson's Disease
QoL	Quality of Life
ROS	Reactive Oxygen Species
SA	South Australia
SLS	Single Leg Stance
TS	Tandem Stance
TUG	Timed Up and Go
UPSIT	University of Pennsylvania Smell Identification Test
WHO	World Health Organisation

Supplementary Information

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Supplementary Material 1: Supplementary Table 1. Individual outcomes for participants before treatment (baseline) and at one-, two-, three-, and five-years

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Author contributions

AL, HK & GeH conceived and organised the five-year assessment; ELL, AL, BB contributed to the study design; AL co-ordinated the study; AL, ST, BB & GeH carried out treatments and assessments in the study; AL, BB & GiH analysed the data; AL & BB prepared the draft manuscript; all authors contributed to, reviewed and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study received human research ethics approval by the Griffith University Human Research Ethics Committee (2018/16), with an extension to 24th April 2024. All participants gave written informed consent prior to taking part in the study. All protocols were approved by the Griffith University Human Research Ethics Committee and were conducted in accordance with their regulations and guidelines.

Consent for publication
Not applicable.

Competing interests
AL and BB are co-founders, and shareholders in SYMBYX Pty Ltd, a med-tech company developing photobiomodulation treatments for neurological disorders. HK and ELL are shareholders in SYMBYX Pty Ltd.

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References

1. Ou Z, Pan J, Tang S, Duan D, Yu D, Nong H, et al. Global trends in the incidence, prevalence, and years lived with disability of Parkinson's disease in 204 countries/territories from 1990 to 2019. Front Public Health. 2021;9:776847.
2. Grünewald A, Kumar KR, Sue CM. New insights into the complex role of mitochondria in Parkinson's disease. Prog Neurobiol. 2019;177:73–93.
3. Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, et al. Update on treatments for nonmotor symptoms of Parkinson's disease—an evidence-based medicine review. Mov Disord. 2019;34(2):180–98.
4. Fox SH, Katzenschlager R, Lim SY, Barton B, de Bie RMA, Seppi K, et al. International Parkinson and movement disorder society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease. Mov Disord. 2018;33(8):1248–66.
5. Lewis MM, Harkins E, Lee EY, Stetter C, Snyder B, Corson T, et al. Clinical progression of Parkinson's Disease: insights from the NINDS Common Data Elements. J Parkinsons Dis. 2020;10(3):1075–85.
6. Morris HR, Spillantini MG, Sue CM, Williams-Gray CH. The pathogenesis of Parkinson's disease. Lancet. 2024;403(10423):293–304.
7. Antonini A, Emmi A, Campagnolo M. Beyond the dopaminergic system: lessons learned from levodopa resistant symptoms in Parkinson's disease. Mov Disorders Clin Pract. 2023;10(Suppl 2):S50.
8. Weaver FM, Follett K, Stern M, Hur K, Harris C, Marks WJ Jr., et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA. 2009;301(1):63–73.
9. Crotty GF, Schwarzschild MA. Chasing Protection in Parkinson's Disease: does Exercise reduce risk and progression? Front Aging Neurosci. 2020;12.
10. Fujikawa J, Morigaki R, Yamamoto N, Oda T, Nakanishi H, Izumi Y et al. Therapeutic devices for motor symptoms in Parkinson's Disease: current progress and a systematic review of recent randomized controlled trials. Front Aging Neurosci. 2022;14.
11. Hamblin MR. Mechanisms and mitochondrial Redox Signaling in Photobiomodulation. Photochem Photobiol. 2018;94(2):199–212.
12. Benson P, Kim JY, Riveros C, Camp A, Johnstone DM. Elucidating the time course of the transcriptomic response to photobiomodulation through gene co-expression analysis. J Photochem Photobiol B. 2020;208:111916.
13. Khan I, Tang E, Arany P. Molecular pathway of near-infrared laser phototoxicity involves ATF-4 orchestrated ER stress. Sci Rep. 2015;5(1):10581.
14. Moro C, Torres N, Arvanitakis K, Cullen K, Chabrol C, Agay D, et al. No evidence for toxicity after long-term photobiomodulation in normal non-human primates. Exp Brain Res. 2017;235(10):3081–92.
15. Cassano P, Caldieraro MA, Norton R, Mischoulon D, Trinh N-H, Nyer M, et al. Reported Side effects, Weight and Blood pressure, after repeated Sessions of Transcranial Photobiomodulation. Photobiomodulation Photomed Laser Surg. 2019;37(10):651–6.
16. Hamblin MR. Mechanisms and applications of the anti-inflammatory effects of photobiomodulation. AIMS Biophys. 2017;4(3):337–61.
17. Dompe C, Moncrieff L, Matys J, Grzech-Leśniak K, Kocherova I, Bryja A, et al. Photobiomodulation-underlying mechanism and clinical applications. J Clin Med. 2020;9(6):1724.
18. Shaikh-Kader A, Houreld NN, editors. Photobiomodulation, cells of connective tissue and repair processes: a look at. Vivo and in Vitro studies on Bone, Cartilage and Tendon cells. Photonics: MDPI; 2022.
19. Zhang R, Qu J. The mechanisms and efficacy of photobiomodulation therapy for arthritis: a comprehensive review. Int J Mol Sci. 2023;24(18):14293.
20. Elad S, Cheng KKF, Lalla RV, Yarom N, Hong C, Logan RM, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer. 2020;126(19):4423–31.
21. Hamblin MR. Photobiomodulation and the brain–has the light dawned? Biochemist. 2016;38(6):24–8.
22. Casalechi HL, Dumont AJL, Ferreira LAB, de Paiva PRV, Machado CSM, de Carvalho PTC, et al. Acute effects of photobiomodulation therapy and magnetic field on functional mobility in stroke survivors: a randomized, sham-controlled, triple-blind, crossover, clinical trial. Lasers Med Sci. 2020;35(6):1253–62.
23. Naeser MA, Zafonte R, Krengel MH, Martin PI, Frazier J, Hamblin MR, et al. Significant improvements in cognitive performance post-transcranial, red/near-infrared light-emitting diode treatments in chronic, mild traumatic brain injury: open-protocol study. J Neurotrauma. 2014;31(11):1008–17.
24. Lamartiniere R, Bergeron R, Aung-Din R, Bennett M, Stephan W, Banas L. Chapter 42 - photobiomodulation treatment for brain disorders: post-traumatic stress disorder (PTSD) and dementia. In: Hamblin MR, Huang Y-Y, editors. Photobiomodulation in the brain. Academic; 2019. pp. 589–97.
25. Schiffer F, Johnston AL, Ravichandran CT, Polcari A, Teicher MH, Webb RH, et al. Psychological benefits 2 and 4 weeks after a single treatment with Near Infrared Light to the forehead: a pilot study of 10 patients with major depression and anxiety. Behavioral Brain Function. 2009;5:46.
26. Saltmarche AE, Naeser MA, Ho KF, Hamblin MR, Lim L. Significant improvement in cognition in mild to moderately severe dementia cases treated with transcranial plus intranasal photobiomodulation: case series report. Photomed Laser Surg. 2017;35(8):432–41.
27. Shaw V, Ashkan K, Benabid A, Stone J, Baker G, Mitrofanis J. Neuroprotection of midbrain dopaminergic cell in MPTP-treated mice after near-infrared light treatment. J Comp Neurol. 2010;518(1):25–40.
28. Purushothuman S, Johnstone D, Nandasena C, Mitrofanis J, Stone J. Photobiomodulation with near infrared light mitigates Alzheimer's disease-related pathology in cerebral cortex - evidence from two transgenic mouse models. Alzheimers Res Ther. 2014;6(1):2.
29. Mitrofanis J. Why and how does light therapy offer neuroprotection in Parkinson's disease? Neural Regeneration Res. 2017;12(4):574.
30. Kim B, Brandli A, Mitrofanis J, Stone J, Purushothuman S, Johnstone DM. Remote tissue conditioning - an emerging approach for inducing body-wide protection against diseases of ageing. Ageing Res Rev. 2017;37:69–78.
31. Ganeshan V, Skladnev NV, Kim JY, Mitrofanis J, Stone J, Johnstone DM. Pre-conditioning with remote photobiomodulation modulates the brain transcriptome and protects against MPTP insult in mice. Neuroscience. 2019;400:85–97.
32. Johnstone DM, Mitrofanis J, Stone J. Targeting the body to protect the brain: inducing neuroprotection with remotely-applied near infrared light. Neural Regen Res. 2015;10(3):349–51.

33. Gordon LC, Johnstone DM. Remote photobiomodulation: an emerging strategy for neuroprotection. Neural Regeneration Res. 2019;14(12):2086.
34. Stone J, Johnstone D, Mitrofanis J, editors. The helmet experiment in Parkinson's disease: an observation of the mechanism of neuroprotection by near infra-red light. 9th WALT Congress (Gold Coast, QLD); 2013.
35. Liebert A, Bicknell B, Laakso EL, Heller G, Jalilitabaei P, Tilley S, et al. Improvements in clinical signs of Parkinson's disease using photobiomodulation: a prospective proof-of-concept study. BMC Neurol. 2021;21(1):256.
36. Liebert A, Bicknell B, Laakso E-L, Tilley S, Pang V, Heller G et al. Improvements in the clinical signs of Parkinson's disease using photobiomodulation: a 3-year follow-up case series. Med Res Archives. 2023;11(3).
37. Bicknell B, Liebert A, Borody T, Herkes G, McLachlan C, Kiat H. Neurodegenerative and neurodevelopmental diseases and the Gut-Brain Axis: the potential of therapeutic targeting of the Microbiome. Int J Mol Sci. 2023;24(11):9577.
38. Gordon LC, Martin KL, Torres N, Benabid AL, Mitrofanis J, Stone J, et al. Remote photobiomodulation targeted at the abdomen or legs provides effective neuroprotection against parkinsonian MPTP insult. Eur J Neurosci. 2023;57(9):1611–24.
39. Joo B, Marquez JL, Osmotherly PG. Ten-second Tandem Stance Test: a potential Tool to assist walking aid prescription and Falls Risk in Balance impaired individuals. Arch Rehabil Res Clin Transl. 2022;4(1):100173.
40. Blodgett JM, Hardy R, Davis D, Peeters G, Kuh D, Cooper R. One-Legged Balance performance and fall risk in Mid and later life: longitudinal evidence from a British birth cohort. Am J Prev Med. 2022;63(6):997–1006.
41. Shumway-Cook A, Brauer S, Woollacott M. Predicting the Probability for Falls in Community-Dwelling older adults using the timed Up & Go Test. Phys Ther. 2000;80(9):896–903.
42. Lang JT, Kassan TO, Devaney LL, Colon-Semenza C, Joseph MF. Test-Retest Reliability and Minimal Detectable Change for the 10-Meter Walk Test in Older Adults With Parkinson's disease. J Geriatr Phys Ther. 2016;39(4).
43. Hill K, Bernhardt J, McGann A, Maltese D, Berkovits D. A new test of dynamic standing balance for stroke patients: reliability, validity, and quantitative clinical tests. Physiotherapy Can. 1996;47:257–62.
44. Pullman SL. Spiral analysis: a new technique for measuring Tremor with a Digitizing Tablet. Mov Disord. 1998;13(S3):85–9.
45. Smithson F, Morris ME, Iansek R. Performance on clinical tests of balance in Parkinson's Disease. Phys Ther. 1998;78(6):577–92.
46. Hile ES, Brach JS, Perera S, Wert DM, VanSwearingen JM, Studenski SA. Interpreting the need for initial support to perform tandem stance tests of balance. Phys Ther. 2012;92(10):1316–28.
47. Muir SW, Berg K, Chesworth B, Klar N, Speechley M. Balance impairment as a risk factor for falls in community-dwelling older adults who are high functioning: a prospective study. Phys Ther. 2010;90(3):338–47.
48. Gill DJ, Freshman A, Blender JA, Ravina B. The Montreal cognitive assessment as a screening tool for cognitive impairment in Parkinson's disease. Mov Disord. 2008;23(7):1043–6.
49. Peto V, Jenkinson C, Fitzpatrick R. PDQ-39: a review of the development, validation and application of a Parkinson's disease quality of life questionnaire and its associated measures. J Neurol. 1998;245(1):S10–4.
50. Chaudhuri KR, Pal S, DiMarco A, Whately-Smith C, Bridgman K, Mathew R, et al. The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2002;73(6):629–35.
51. Holden SK, Finseth T, Sillau SH, Berman BD. Progression of MDS-UPDRS scores over five years in De Novo Parkinson Disease from the Parkinson's progression markers Initiative Cohort. Mov Disorders Clin Pract. 2018;5(1):47–53.
52. Foltynie T, Athauda D. Chapter 13 - Repurposing anti-diabetic drugs for the treatment of Parkinson's disease: Rationale and clinical experience. In: Björklund A, Cenci MA, editors. Progress in Brain Research. Volume 252. Elsevier; 2020. pp. 493–523.
53. Kent AL, Broom M, Parr V, Essex RW, Abdel-Latif ME, Dahlstrom JE, et al. A safety and feasibility study of the use of 670 nm red light in premature neonates. J Perinatol. 2015;35(7):493–6.
54. Bensadoun RJ, Epstein JB, Nair RG, Barasch A, Raber-Durlacher JE, Migliorati C, et al. Safety and efficacy of photobiomodulation therapy in oncology: a systematic review. Cancer Med. 2020;9(22):8279–300.
55. Cassano P, Norton R, Caldieraro MA, Vahedifard F, Vizcaino F, McEachern KM, et al. Tolerability and safety of transcranial photobiomodulation for mood and anxiety disorders. Photonics. 2022;9(8):507.
56. Herkes G, McGee C, Liebert A, Bicknell B, Isaac A, Kiat H et al. A novel transcranial photobiomodulation device to address motor signs of Parkinson's disease: a parallel randomised feasibility study. EClinicalMedicine. 2023;66.
57. Ishida C, Takahashi K, Kato-Motozaki Y, Tagami A, Komai K. Effectiveness of Levodopa in patients with multiple system atrophy and Associated Clinicopathological features. Intern Med. 2021;60(3):367–72.
58. Stankovic I, Fanciulli A, Sidoroff V, Wenning GK. A review on the clinical diagnosis of multiple system atrophy. Cerebellum. 2023;22(5):825–39.
59. Lidstone SC, Schulzer M, Dinelle K, Mak E, Sossi V, Ruth TJ, et al. Effects of expectation on placebo-induced dopamine release in Parkinson disease. Arch Gen Psychiatry. 2010;67(8):857–65.
60. Quattrone A, Barbagallo G, Cerasa A, Stoessl AJ. Neurobiology of placebo effect in Parkinson's disease: what we have learned and where we are going. Mov Disord. 2018;33(8):1213–27.
61. Bullock-Saxton J, Lehn A, Laakso E. Exploring the effect of combined transcranial and intra-oral photobiomodulation therapy over a four-week period on physical and cognitive outcome measures for people with Parkinson's disease: a randomized double-blind placebo-controlled pilot study. J Alzheimers Dis. 2021;83(4):1499–512.
62. McGee C, Liebert A, Bicknell B, Pang V, Isaac V, McLachlan CS, et al. A randomized placebo-controlled study of a Transcranial Photobiomodulation Helmet in Parkinson's Disease: post-hoc analysis of Motor outcomes. J Clin Med. 2023;12(8):2846.
63. Goetz CG, Leurgans S, Raman R. Placebo-associated improvements in motor function: comparison of subjective and objective sections of the UPDRS in early Parkinson's disease. Mov Disord. 2002;17(2):283–8.
64. Goetz CG, Wuu J, McDermott MP, Adler CH, Fahn S, Freed CR, et al. Placebo response in Parkinson's disease: comparisons among 11 trials covering medical and surgical interventions. Mov Disord. 2008;23(5):690–9.
65. Pagano G, Taylor KI, Anzures Cabrera J, Simuni T, Marek K, Postuma RB, et al. Prasinezumab slows motor progression in rapidly progressing early-stage Parkinson's disease. Nat Med. 2024;30(4):1096–103.
66. Limousin P, Foltynie T. Long-term outcomes of deep brain stimulation in Parkinson disease. Nat Reviews Neurol. 2019;15(4):234–42.
67. Aarsland D, Creese B, Politis M, Chaudhuri KR, ffytche DH, Weintraub D, et al. Cognitive decline in Parkinson disease. Nat Reviews Neurol. 2017;13(4):217–31.
68. Tsukita K, Sakamaki-Tsukita H, Takahashi R. Long-term effect of regular physical activity and Exercise habits in patients with early Parkinson Disease. Neurology. 2022;98(8):e859–71.
69. Tucak C, Chih H, Mastaglia F, Rodrigues J. The 'PD Warrior' exercise program improves motor outcomes and quality of life in patients with early Parkinson's disease: results of a pilot study. Intern Med J. 2023;n/a(n/a):1–10.
70. Afshari M, Yang A, Bega D. Motivators and barriers to Exercise in Parkinson's Disease. J Parkinsons Dis. 2017;7(4):703–11.
71. Schootemeijer S, Van Der Kolk NM, Ellis T, Mirelman A, Nieuwboer A, Nieuwhof F, et al. Barriers and motivators to engage in exercise for persons with Parkinson's disease. J Parkinson's Disease. 2020;10(4):1293–9.
72. Dutra YM, Malta ES, Elias AS, Broatch JR, Zagatto AM. Deconstructing the ergogenic effects of photobiomodulation: a systematic review and meta-analysis of its efficacy in improving mode-specific exercise performance in humans. Sports Med. 2022;52(11):2733–57.
73. De Oliveira MF, Johnson DS, Demchak T, Tomazoni SS, Ernesto C. Low-intensity LASER and LED (photobiomodulation therapy) for pain control of the most common musculoskeletal conditions. Eur J Phys Rehabil Med. 2022;58(2):282.
74. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disorders: Official J Mov Disorder Soc. 2008;23(15):2129–70.
75. Charroud C, Turella L. Subcortical grey matter changes associated with motor symptoms evaluated by the Unified Parkinson's disease rating scale (part III): a longitudinal study in Parkinson's disease. NeuroImage: Clin. 2021;31:102745.
76. Schrag A, Dodel R, Spottke A, Bornschein B, Siebert U, Quinn NP. Rate of clinical progression in Parkinson's disease. A prospective study. Mov Disord. 2007;22(7):938–45.
77. Lawton M, Ben-Shlomo Y, May MT, Baig F, Barber TR, Klein JC, et al. Developing and validating Parkinson's disease subtypes and their motor and cognitive progression. J Neurol Neurosurg Psychiatry. 2018;89(12):1279–87.
78. Alves G, Wentzel-Larsen T, Aarsland D, Larsen JP. Progression of motor impairment and disability in Parkinson disease. Neurology. 2005;65(9):1436–41.
79. Mollenhauer B, Zimmermann J, Sixel-Döring F, Focke NK, Wicke T, Ebentheuer J, et al. Baseline predictors for progression 4 years after Parkinson's disease diagnosis in the De Novo Parkinson Cohort (DeNoPa). Mov Disord. 2019;34(1):67–77.

80. Helmy A, Hamid E, Salama M, Gaber A, El-Belkimy M, Shalash A. Baseline predictors of progression of Parkinson's disease in a sample of Egyptian patients: clinical and biochemical. Egypt J Neurol Psychiatry Neurosurg. 2022;58(1):1–10.
81. Jankovic J, Kapadia AS. Functional decline in Parkinson disease. Arch Neurol. 2001;58(10):1611–5.
82. Merola A, Espay AJ, Romagnolo A, Bernardini A, Rizzi L, Rosso M, et al. Advanced therapies in Parkinson's disease: long-term retrospective study. Parkinsonism Relat Disord. 2016;29:104–8.
83. Markopoulou K, Aasly J, Chung SJ, Dardiotis E, Wirdefeldt K, Premkumar AP, et al. Longitudinal monitoring of Parkinson's disease in different ethnic cohorts: the DodoNA and LONG-PD study. Front Neurol. 2020;11:548.
84. Bartl M, Dakna M, Schade S, Wicke T, Lang E, Ebentheuer J, et al. Longitudinal change and progression indicators using the Movement Disorder Society-Unified Parkinson's Disease Rating Scale in two independent cohorts with early Parkinson's Disease. J Parkinson's Disease. 2022;12:437–52.
85. Horváth K, Aschermann Z, Kovács M, Makkos A, Harmat M, Janszky J, et al. Minimal clinically important differences for the experiences of daily living parts of movement disorder society–sponsored unified Parkinson's disease rating scale. Mov Disord. 2017;32(5):789–93.
86. Bloem BR, Grimbergen YAM, Cramer M, Willemsen M, Zwinderman AH. Prospective assessment of falls in Parkinson's disease. J Neurol. 2001;248(11):950–8.
87. Allen NE, Schwarzel AK, Canning CG. Recurrent falls in Parkinson's disease: a systematic review. Parkinson's disease. 2013;2013.
88. Morris S, Morris ME, Iansek R. Reliability of measurements obtained with the timed up & go test in people with Parkinson disease. Phys Ther. 2001;81(2):810–8.
89. Paker N, Bugdayci D, Goksenoglu G, Demircioğlu DT, Kesiktas N, Ince N. Gait speed and related factors in Parkinson's disease. J Phys Therapy Sci. 2015;27(12):3675–9.
90. Bryant M, Rintala D, Hou J, Lai E, Protas E. Effects of levodopa on forward and backward gait patterns in persons with Parkinson's disease. NeuroRehabilitation. 2011;29(3):247–52.
91. Galna B, Lord S, Burn DJ, Rochester L. Progression of gait dysfunction in incident Parkinson's disease: impact of medication and phenotype. Mov Disord. 2015;30(3):359–67.
92. Rochester L, Galna B, Lord S, Yarnall AJ, Morris R, Duncan G, et al. Decrease in Aβ42 predicts dopa-resistant gait progression in early Parkinson disease. Neurology. 2017;88(16):1501–11.
93. Cavanaugh JT, Ellis TD, Earhart GM, Ford MP, Foreman KB, Dibble LE. Toward understanding ambulatory activity decline in Parkinson disease. Phys Ther. 2015;95(8):1142–50.
94. Wilson J, Alcock L, Yarnall AJ, Lord S, Lawson RA, Morris R, et al. Gait Progression over 6 years in Parkinson's Disease: effects of Age, Medication, and Pathology. Front Aging Neurosci. 2020;12:577435.
95. Steffen T, Seney M. Test-retest reliability and minimal detectable change on balance and ambulation tests, the 36-item short-form health survey, and the unified Parkinson disease rating scale in people with parkinsonism. Phys Ther. 2008;88(6):733–46.
96. Hass CJ, Bishop M, Moscovich M, Stegemöller EL, Skinner J, Malaty IA, et al. Defining the clinically meaningful difference in gait speed in persons with Parkinson disease. J Neurol Phys Ther. 2014;38(4):233–8.
97. Sebastia-Amat S, Tortosa-Martínez J, García-Jaén M, Pueo B. Within-subject variation in the cognitive timed up and go test as an explanatory variable in fall risk in patients with parkinson's disease. J Rehabil Med. 2021;53(10):jrm00234.
98. Çekok K, Kahraman T, Duran G, Çolakoğlu BD, Yener G, Yerlikaya D et al. Timed up and go Test with a Cognitive Task: correlations with neuropsychological measures in people with Parkinson's Disease. Cureus. 2020;12(9).
99. Nocera JR, Stegemöller EL, Malaty IA, Okun MS, Marsiske M, Hass CJ. Using the timed up & go test in a clinical setting to predict falling in Parkinson's disease. Arch Phys Med Rehabil. 2013;94(7):1300–5.
100. Huang S-L, Hsieh C-L, Wu R-M, Tai C-H, Lin C-H, Lu W-S. Minimal detectable change of the timed Up & Go Test and the dynamic Gait Index in People with Parkinson Disease. Phys Ther. 2011;91(1):114–21.
101. Chen YA, Wu RM, Sheu CH, Lin CH, Huang CY. Attentional focus effect on dual-task walking in Parkinson's disease with and without freezing of gait. Geroscience. 2023;45(1):177–95.
102. Lima LC, Ansai JH, Andrade LP, Takahashi AC. The relationship between dual-task and cognitive performance among elderly participants who exercise regularly. Braz J Phys Ther. 2015;19(2):159–66.
103. Winser SJ, Kannan P, Bello UM, Whitney SL. Measures of balance and falls risk prediction in people with Parkinson's disease: a systematic review of psychometric properties. Clin Rehabil. 2019;33(12):1949–62.
104. Rahmati Z, Behzadipour S, Schouten AC, Taghizadeh G, Firoozbakhsh K. Postural control learning dynamics in Parkinson's disease: early improvement with plateau in stability, and continuous progression in flexibility and mobility. Biomed Eng Online. 2020;19:1–22.
105. Zhang C, Talaber A, Truong M, Vargas BB. K-D balance: an objective measure of balance in tandem and double leg stances. Digit Health. 2019;5:2055207619885573.
106. Agrawal Y, Carey JP, Hoffman HJ, Sklare DA, Schubert MC. The modified Romberg Balance Test: normative data in U.S. adults. Otol Neurotol. 2011;32(8):1309–11.
107. Springer BA, Marin R, Cyhan T, Roberts H, Gill NW. Normative values for the unipedal stance test with eyes open and closed. J Geriatr Phys Ther. 2007;30(1):8–15.
108. Santangelo G, Vitale C, Picillo M, Moccia M, Cuoco S, Longo K, et al. Mild cognitive impairment in newly diagnosed Parkinson's disease: a longitudinal prospective study. Parkinsonism Relat Disord. 2015;21(10):1219–26.
109. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sørensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol. 2003;60(3):387–92.
110. Roheger M, Kalbe E, Liepelt-Scarfone I. Progression of cognitive decline in Parkinson's disease. J Parkinson's Disease. 2018;8(2):183–93.
111. Wills A-MA, Elm JJ, Ye R, Chou KL, Parashos SA, Hauser RA, et al. Cognitive function in 1736 participants in NINDS exploratory trials in PD Long-term Study-1. Parkinsonism Relat Disord. 2016;33:127–33.
112. Broeders M, Velseboer DC, de Bie R, Speelman JD, Muslimovic D, Post B, et al. Cognitive change in newly-diagnosed patients with Parkinson's disease: a 5-year follow-up study. J Int Neuropsychol Soc. 2013;19(6):695–708.
113. Aarsland D, Andersen K, Larsen JP, Perry R, Wentzel-Larsen T, Lolk A, et al. The rate of Cognitive decline in Parkinson Disease. Arch Neurol. 2004;61(12):1906–11.
114. Greenland JC, Camacho M, Williams-Gray CH. Chapter 12 - The dilemma between milestones of progression versus clinical scales in Parkinson's disease. In: Espay AJ, editor. Handbook of clinical neurology. Volume 192. Elsevier; 2023. pp. 169–85.
115. Krishnan K, Rossetti H, Hynan LS, Carter K, Falkowski J, Lacritz L, et al. Changes in Montreal Cognitive Assessment scores over time. Assessment. 2017;24(6):772–7.
116. Parashos SA, Luo S, Biglan KM, Bodis-Wollner I, He B, Liang GS, et al. Measuring disease progression in early Parkinson disease: the National Institutes of Health Exploratory Trials in Parkinson Disease (NET-PD) experience. JAMA Neurol. 2014;71(6):710–6.
117. Margolius A, Cubillos F, He Y, Wu S, Schmidt P, Simuni T. Predictors of clinically meaningful change in PDQ-39 in Parkinson's disease. Parkinsonism Relat Disord. 2018;56:93–7.
118. Horváth K, Aschermann Z, Kovács M, Makkos A, Harmat M, Janszky J, et al. Changes in quality of life in Parkinson's Disease: how large must they be to be relevant? Neuroepidemiology. 2017;48(1–2):1–8.
119. Kharkar S, Ellenbogen JR, Samuel M, Rizos A, Silverdale M, Chaudhuri KR, et al. Changes in Parkinson's disease sleep symptoms and daytime somnolence after bilateral subthalamic deep brain stimulation in Parkinson's disease. Npj Parkinson's Disease. 2018;4(1):16.
120. Dan X, Wechter N, Gray S, Mohanty JG, Croteau DL, Bohr VA. Olfactory dysfunction in aging and neurodegenerative diseases. Ageing Res Rev. 2021;70:101416.
121. Sasaki S, Horie Y. Association between Olfactory Impairment and Disease Severity and Duration in Parkinson's Disease. Mov Disorders Clin Pract. 2020;7(7):820–6.
122. Suzuki H, Teranishi M, Katayama N, Nakashima T, Sugiura S, Sone M. Relationship between cognitive impairment and olfactory function among older adults with olfactory impairment. Auris Nasus Larynx. 2021;48(3):420–7.
123. Tarakad A, Jankovic J. Chapter Seventeen - Anosmia and Ageusia in Parkinson's Disease. In: Chaudhuri KR, Titova N, editors. International Review of Neurobiology. Volume 133. Academic; 2017. pp. 541–56.
124. Liebert A, Bicknell B, Laakso E-L, Jalilitabaei P, Tilley S, Kiat H, et al. Remote Photobiomodulation treatment for the clinical signs of Parkinson's Disease: a Case Series Conducted during COVID-19. Photobiomodulation Photomed Laser Surg. 2022;40(2):112–22.

125. Liebert A, Saltmarche A, McGonaghy M, Hares O, Bicknell B, Herkes G. Photobiomodulation as part of a multi-disciplinary approach for the treatment of Parkinson's disease symptoms. Medical Research Archives. 2024;in press.
126. Salehpour F, Hamblin MR, DiDuro JO. Rapid reversal of cognitive decline, olfactory dysfunction, and quality of life using multi-modality photobiomodulation therapy: case report. Photobiomodulation, photomedicine, and laser surgery. 2019;37(3):159–67.
127. Hamilton C, Hamilton D, Nicklason F, Mitrofanis J. Transcranial photobiomodulation therapy: observations from four movement disorder patients. In: Caldieraro M, Cassano P, editors. Photobiomodulation in the Brain: Elsevier; 2019. pp. 463 – 72.
128. Panhoca VH, Ferreira LT, de Souza VB, Ferreira SA, Simão G, de Aquino Junior AE, et al. Can photobiomodulation restore anosmia and ageusia induced by COVID-19? A pilot clinical study. J Biophotonics. 2023;16(6):e202300003.

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