Dementia Symptom Reduction with Weak Trans-Cranial Ultrasound Treatment: A Pilot Study

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Abstract
We examined the effects of pulsed ultrasound treatment, when combined with standard medications, on patients with cognitive impairment, including effects on the behavioral and psychological symptoms of dementia, motor deficits, and cognitive dysfunction.
A 12-week-long low-intensity pulsed ultrasound (LIPUS) protocol was applied, without medication regimen changes, on three patients with poorly controlled dementia with Lewy bodies (DLB), two Alzheimer's type dementia (ATD) patients with severely impaired cognitive function, and three Parkinson's disease with dementia (PDD) patients with severe motor deficits. Symptom severity and caregiver burden were assessed using the Neuropsychiatric Inventory Questionnaire (NPI-Q). In addition, interview-based assessments of cognitive function and the Mini-Mental State Examination (MMSE) were used. The NPI-Q and MMSE revealed a positive effect of the combination of ultrasound and medication therapies on symptoms in six and seven out of the eight patients, respectively. These results suggest that pulsed ultrasound, when combined with medication, may be effective for improving cognitive function in patients with under-treated dementia.

Keywords: ultrasound, dementia, behavioral and psychological symptoms of dementia (BPSD), the Neuropsychiatric Inventory Questionnaire (NPI-Q), the Mini-Mental State Examination (MMSE)

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1. Introduction

In the near future, elderly individuals, who are defined as those aged ≥65 years, are expected to grow to 27.7% of the total population of Japan [1]. The number of people with age-related dementia will exceed 7 million in Japan, constituting one affected individual out of every five elderly people [2]; therefore, it has become a critical public health concern [3,4].

We focused on the three categories of dementia namely dementia with Lewy bodies (DLB), Alzheimer's type dementia (ATD), and Parkinson's disease with dementia (PDD) in this study. DLB patients may experience optical illusions, disorientation, inconsistent states of consciousness, Parkinson's disease symptoms, depression, and disordered rapid eye movement (REM) sleep. ATD patients may experience disordered memory, defective judgment, disorientation, inability to understand language, impatience, flushing, violent impulses, delusions, depression, and a lack of motivation. PDD patients may experience poor motor coordination, tremors, muscle rigidity, hypokinesia, postural reflexes, lack of facial expression, poor verbal pronunciation, illiteracy, reduced motor skills as well as impairment of thought processes, mental function and memory.

The quality of life (QOL) of both the patient and caregiver is significantly and negatively impacted by

dementia. Additionally, partners of patients with dementia may themselves also be elderly, rendering them unable to take care of their partners properly due to their own declining health [5-9]. In addition, due to declines in the birth rate, adequately staffing nursing homes to care for these individuals with dementia has also become a serious issue in Japan [10,11].

There are many therapeutic agents and treatment strategies for the prevention and treatment of dementia. Both pharmacological and non-pharmacological therapies have been developed and assessed to provide clinicians with better tools to treat their dementia patients, as well as to improve the understanding of disease etiology and pathogenesis [12-18].

With the approval of medications such as acetylcholinesterase inhibitors and NMDA receptor antagonists, pharmacotherapeutic strategies for the prevention of dementia's progression have gained popularity [19-23]. However, there is an increasing need for non-pharmacological therapies to augment the treatment of patients who are taking the maximum medication dose. It is critical that these additional non-pharmacological therapies cause no side effects and lead to long-term symptomatic improvement. Recently, cognitive training [24-27], music therapy [28-34], aromatherapy, and massage [35-44] and exercise therapy [45-51] have attracted attention as symptomatic treatments for dementia.

While animal studies have examined the effects of ultrasound devices [51-55] and ultrasound therapy on dementia-like phenotypes, similar studies in humans have not been performed. Therefore, we conducted a study in healthy individuals ten years ago using a novel ultrasonic head massager. The device, which was found to be physically safe [56], promoted cerebral blood flow [57] in healthy individuals. Based on these results, the present study examined the beneficial effects of pulsed ultrasound treatment (twice a day for 12 consecutive weeks), combined with standing medications, on symptoms in patients with DLB, ATD, and PDD.

2. Materials and Methods

2-1. Device

A low-intensity, low-frequency pulsed ultrasound device (ULTRA-MA; Kamiyama Mfg. Co., Ltd., Chiba, Japan) developed by our team was used for ultrasound stimulation. Figure 1 depicts how the device was worn (Fig.1 A) and the positions of the ultrasound transducers (Fig.1 B) and control device (Fig.1 C). Briefly, a headband-like device with ultrasound transducers was gently wrapped around the top of the head. Depending on symptom severity, two (Type A: 2 in the lateral frontal area) or four (Type B: 2 on the frontal area and 2 on the temporal area) ultrasound transducers were used on the patients. The ultrasound frequency was ≤ 30 kHz $\pm$ 5% and the maximum ultrasound intensity was 1.6 mW/cm^2. The mean maximum ultrasound power per transducer was 1.6 mW/sec. The modulated pulse rate was 10% $\pm$ 1%.

2-2. Subjects

Subjects included patients with a definitive dementia diagnosis, as previously described, according to a medical interview, imaging test [magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), or myocardial scintigraphy], or cognitive functioning test. Patients were asked to continue any ongoing pharmacological treatment and were able to provide informed consent prior to their participation in the study, except for one with severe dementia who was unable to understand language and provided informed consent via a relative. All other subjects were able to provide informed consent. Patients who did not meet the exclusion criteria (listed below) were included.

The exclusion criteria were as follows:

- Could not undergo tests such as the Neuropsychiatric Inventory Questionnaire (NPI-Q), Mini-Mental State Examination (MMSE) due to visual or hearing impairment and aphasia.
- Severe or poorly managed disease at study onset.

- An implanted medical electrical device susceptible to electromagnetic interference (e.g., cardiac pacemaker, implantable defibrillator, etc.).
- Any intracranially implanted electrodes.
- Use of an in-ear hearing aid.
- Deemed ineligible by a physician.

A total of eight subjects were divided into the following three groups, as shown in Table 1:
- Group 1: three DLB patients
- Group 2: two ATD patients
- Group 3: three PDD patients

2-3. Procedures

After receiving face-to-face instructions from the physician on how to use the ultrasound device, each patient was provided with a device to use at home. Given that dementia affects memory and comprehension, a relative was trained on how to use the device and agreed to supervise its use at home. Patients were instructed to use the device twice daily at a maximum ultrasound intensity of 1.6 mW/cm^2 for 20 minutes for 12 consecutive weeks. This protocol remained the same throughout the study period.

All patients underwent medical interviews at the first (week 0), second (week 4), third (week 8), and fourth (week 12) visits. At each visit, patients completed the NPI-Q (to test behavioral and psychological symptom severity and caregiver burden; minimum score of 0, maximum score of 50) and MMSE (to test cognitive function; minimum score of 0, maximum score of 30). All results are presented as pre-to-post-treatment changes in test scores at weeks 0, 4, 8, and 12.

Patients with PDD also underwent a further Parkinson's-specific assessment [58,59].

The follow-up period spanned from June 2017 to March 2018.

This study was approved by the ethics committee of the Folkmore Medical Corporation Clinic Ian Center Minami on February 13, 2017.

3. Results

3-1. Group 1 (DLB patients)

Three patients with several behavioral and psychological symptoms of dementia (BPSD) and a definitive dementia diagnosis [DLB or Lewy body disease (LBD) [60]] were included in these analyses. LBD is a chronic progressive neuropsychiatric disorder, which is clinically characterized by Parkinson symptoms of presenile, senile, or sometimes younger onset dementia.

The type A device was used by all patients in Group 1. Table 1 shows all patient data, while Table 2 and Figure 3 (A, B, and C) show their NPI-Q and MMSE scores. Although the BPSD symptoms (e.g., visual hallucinations, vertigo and depression) improved, severe Capgras syndrome (i.e., misidentification of familiar persons as strangers in disguise) persisted in patient DLB-1. As a result, this patient's symptom severity and caregiver burden scores increased from 4 to 7 points and from 5 to 9 points, respectively. MMSE scores (an assessment of cognitive function) improved by 8 points from 18 points (week 0) to 26 points (week 12).

Patient DLB-1 NPI-Q patient severity:	4→7 (deterioration)
Patient DLB-1 NPI-Q caregiver burden:	5→9 (deterioration)
Patient DLB-1 MMSE cognitive function:	18→26 (improvement)

Patient DLB-2 presented with severe dizziness on standing up, disordered REM sleep, depression symptoms, and memory impairments, all of which improved with treatment. This patient's symptom

severity and caregiver burden scores improved from 5 to 2 points and from 4 to 0 points, respectively, with treatment. The patient's MMSE scores also improved from 26 to 30 points and cognitive symptoms were absent by week 4.

Patient DLB-2 NPI-Q patient severity:	5→2 (improvement)
Patient DLB-2 NPI-Q caregiver burden:	4→ 0 (improvement)
Patient DLB-2 MMSE cognitive function:	26→ 30 (improvement)

Patient DLB-3 presented with disordered REM sleep, severe depression symptoms, and cognitive dysfunction, all of which greatly improved with treatment. The patient severity and caregiver burden (per the NPI-Q) both improved from 3 to 0 points. This patient's BPSDs were absent by week 4, MMSE scores improved from 29 to 30 points, and cognitive symptoms were absent by week 8.

Patient DLB-3 NPI-Q patient severity:	3→0 (improvement)
Patient DLB-3 NPI-Q caregiver burden:	3→0 (improvement)
Patient DLB-3 MMSE cognitive function:	29→30 (improvement)

Patient DLB-2 had the highest number of BPSDs of the three patients included in this group. Patient DLB-2 also exhibited sleep disturbances in 2003, vertigo in 2008, arrhythmia in 2010, depression in 2013, brain atrophy in 2014, and was diagnosed with memory impairments in 2017. Since being diagnosed with DLB (MMSE score: 22) in January 2017, he continued to take Aricept (Donepezil Hydrochloride Tablet, 5 mg) and Tsumura Yokukansankachimpihange (a liver-function inhibitor composed of tangerine peels and *Pinellia* Tuber) extract granules. Below is an expert from the patient's weekly observational case study diary:
W0: Feeling excited on day 1
W1: Symptoms were absent (disordered REM sleep, dizziness on standing up, and gradual improvement in forgetfulness and impaired concentration)
W4: Similar to week 1
W8: Stable condition. In addition, in terms of forgetfulness, this patient remembered and understood what he read in the newspaper.
W12: Writing ability recovered

This diary demonstrates the improvements in dementia symptoms in this patient with device use. After confirming these symptom improvements using the MMSE scores and by making broad comparisons across group 1, we conducted an observational study on patients with ATD.

3-2. Group 2 (ATD patients)

Two patients, who were diagnosed by a specialist with moderate or severe ATD, were included in Group 2 and used the type A device. Table 1 shows data on the patient, while Table 2 and Figure 3 D, E, and F show their NPI-Q and MMSE scores. As in group 1, BPSDs in group 2 were substantially improved.

Patient ATD-1's depression symptoms greatly improved. The patient's symptom severity and caregiver burden (per the NPI-Q) also improved considerably from 3 to 1 point and from 2 to 0 points, respectively. MMSE scores also improved from 18 to 20 points.

Patient ATD-1 NPI-Q patient severity:	3→1 (improvement)
Patient ATD-1 NPI-Q caregiver burden:	2→0 (improvement)
Patient ATD-1 MMSE cognitive function:	18→20 (improvement)

Patient ATD-2's symptom severity and caregiver burden per the NPI-Q also dramatically improved from 8 to 0 points and from 12 to 0 points, respectively. Both symptoms were absent by week 4. This patient's MMSE score also improved from 7 to 11 points. This patient experienced stable sleep without using sleeping pills, and BPSDs (e.g., wondering, violent language, and yelling etc.) also substantially improved.

Patient ATD-2 NPI-Q patient severity:	8→0 (improvement)
Patient ATD-2 NPI-Q caregiver burden:	12→ 0 (improvement)
Patient ATD-2 MMSE cognitive function:	7→ 11 (improvement)

3-3. Group 3 (PDD patients)

Three patients with definitive specialist diagnoses of DLB with severe Parkinsonism or Parkinson's disease with dementia (PDD); and with severe or frequent symptoms (e.g., tremor, muscle rigidity, akinesia/hypokinesia, and postural reflexivity) were included in these analyses.

Patients in Group 3 utilized the two types of devices, as follows:

- Patient PDD-1: Type A device
- Patient PDD-2: Type A until week 4, then Type B device
- Patient PDD-3: Type B device

Table 1 shows data on the patients while Table 2 and Figure 3 G, H, and I show the NPI-Q and MMSE scores of patients in this group. Patient PDD-1's Parkinsonism symptoms (i.e., tremor, muscle rigidity, akinesia and hypokinesia, and postural reflexivity) and BPSDs (i.e., depression, fatigue, symptoms of dyspnea) improved after 12 weeks. Patient severity and caregiver burden, per the NPI-Q, significantly improved from 4 to 0 points and 4 to 0 points, respectively. Both symptoms were absent by week 12. Furthermore, this patient's MMSE scores improved by 7 points, from 22 to 29 points.

Patient PDD-1 NPI-Q patient severity:	4→0 (improvement)
Patient PDD-1 NPI-Q caregiver burden:	4→0 (improvement)
Patient PDD-1 MMSE cognitive function:	22→29 (improvement)

PDD-2's Parkinsonism symptoms (i.e., tremor, muscle rigidity, akinesia and hypokinesia, postural reflexivity) improved after 12 weeks, as shown in Table 1. While some BPSDs (i.e., depression, difficulty with breathing, and no appetite) improved, no improvement was seen in visual hallucinations. This patient's NPI-Q score also decreased from 3 (week 0) to 1 point (weeks 4 and 8), and then increased again to 3 points (week 12). On the other hand, the patient's caregiver burden score increased from 3 to 5 points. This may be due to this patient's discontinuation of Artane medication during the study. This patient's visual hallucinations also became more common, reducing his NPI-Q scores. Finally, this patient's MMSE scores improved from 24 to 30 points and cognitive symptoms fully resolved by week 12.

Patient PDD-2 NPI-Q patient severity:	3→3 (improvement)
Patient PDD-2 NPI-Q caregiver burden:	3→ 5 (deterioration)
Patient PDD-2 MMSE cognitive function:	24→ 30 (improvement)

Patient PDD-3's Parkinsonism symptoms (i.e., tremor, muscle rigidity, akinesia and hypokinesia, and postural reflexivity) improved after 12 weeks of treatment. Patient symptom severity and caregiver burden, per the NPI-Q, dramatically improved from 5 to 0 points and from 8 to 0 points, respectively, and were absent by weeks 8 and 4, respectively. This patient's MMSE scores decreased by 4 points,

from 24 points (week 0) to 20 points (week 12), evidencing decreased cognitive function during the study period.

Patient PDD-3 NPI-Q patient severity:	5→0 (improvement)
Patient PDD-3 NPI-Q caregiver burden:	8→0 (improvement)
Patient PDD-3 MMSE cognitive function:	24→20 (deterioration)

4. Discussion

We conducted a pilot study on the possible effects of ultrasound on dementia in DLB, ATD and PDD patients.

After 12 weeks of treatment, MMSE scores improved in all three DLB patients (Group 1). NPI-Q scores also improved in two patients in this group after 12 weeks. Symptom alleviation/improvement was recognized by patients, caregivers, and cohabitating family members. Patient DLB-1, who saw no improvement in NPI-Q scores, did see improvement in Capgras symptoms (symptom severity/frequency), as noted by the patient's family members, attending physicians, and caregivers. Despite this patient's NPI-Q raw scores decreasing, improvement in his Capgras symptoms greatly improved the caregiver's level of burden at some point. Group 1 saw an improvement in BPSD (NPI-Q) and cognitive symptoms (MMSE) and no adverse events due to drug administration. This result suggests that low-intensity pulsed ultrasound (LIPUS), combined with appropriate dementia medications, is probably effective in reducing BPSD regardless of the severity or frequency of the symptoms. In addition, LIPUS combined with medication at the maximum dose caused no side effects and led to long-term symptom improvement in the patients. Given that the majority of cases examined here exhibited improved symptoms by week 4, extending treatment beyond 12 weeks may provide sustained, beneficial effects (one-year follow-up data not shown here).

Additionally, we found that LIPUS led to improved sleep quality, daytime QOL (e.g., less wandering, outbursts, less irritability, etc.), mood, and NPI-Q scores in two ATD patients (Group 2). Furthermore, although improvements in these symptoms were small, the MMSE scores improved considerably. These differences may be due to different mechanisms and affected sites in each dementia patient [61-63]. Future clinical trials should primarily be done using larger patient samples and could also include other diagnostic techniques such as positron emission tomography (PET) [64].

Furthermore, LIPUS was applied in patients with Parkinsonism (Group 3) to examine its effects on motor symptoms and found improvements in Parkinson's disease (PD) symptoms (e.g., tremor, muscle rigidity, akinesia and hypokinesia, and postural reflexivity). Figure 2 shows the results of spontaneous writing and figure copying tasks on the MMSE in patient PDD-3. Although this patient could not write anything on a blank sheet of paper at the start of treatment, by week 8, they were able to write and draw some. By week 12, the patient was able to write a sentence and draw two pentagons, although these were small in size. The patient also felt an improvement in his Parkinsonism. In addition, the patient's motor functioning improved, per the NPI-Q scores. Given this, the patient was able to dress and undress themselves (e.g., fasten buttons) without assistance, and thus reducing caregiver burden. In addition, the patient's raw MMSE scores also improved. However, in patient PDD-2, the discontinuation of dementia medication after an initial trend toward recovery led to visual hallucinations, although cognitive and motor function remained good.

As shown in Figure 3, NPI-Q (patient severity and caregiver burden) and MMSE scores changed at each time point in all patients except for patient DLB-1. Furthermore, NPI-Q patient severity consistently improved after week 4. Although NPI-Q caregiver burden was not always concomitant with symptom improvements, it did improve in 5 out of 8 patients. Moreover, in all patients except patient PDD-3, MMSE scores greatly improved after the start of treatment.

Our findings also indicate that Type B devices (four oscillators across the frontal and temporal areas) provide more stimuli, and thus are more effective than Type A devices in improving motor function symptoms [63] specific to PD. However, Type A devices (two oscillators on the frontal area) considerably improved BPSD and cognitive symptoms.

As described above, the present observational study demonstrated the safety and effectiveness of LIPUS devices, in combination with medication, in improving BPSD, cognitive, and motor function symptoms in dementia patients.

Considering the various symptoms present in each dementia patient, the difficulties in adequately prescribing medications to these patients (e.g., due to medication hypersensitivity, inefficacy, etc.), and the severity of symptoms, including difficulties completing daily activities and reduced cognitive function, our approach could contribute to an improved individualized dementia treatment, relief of burden on family members and caregivers, and improvement in QOL [5-9].

There are several limitations to this study including the small sample size. Moreover, we did not determine the length of duration of improvements of dementia symptoms after the cycle of LIPUS sessions, or the patients' tolerance to medium and long-term application of LIPUS. Despite this, our research revealed a dramatic effect of ultrasound stimulation on dementia symptoms. As the present was a pilot study, future, larger studies considering NPI-Q severity and disease onset should further examine the effects of LIPUS when combined with medication-based therapies (e.g., in hybrid therapy) to substantiate these pilot findings further. The findings of these studies may possibly lead to critical and significant improvements in the treatment options available to individuals with dementia and their caregivers/families.

5. Conclusion

The present study demonstrates that whole-brain LIPUS, when combined with existing dementia medications, has immediate effects on improving symptoms, and thus easing the load on caregivers of dementia patients. Critically, we found no adverse effects of the effective dosage of LIPUS for treating BPSDs. This lack of side effects may allow long-term application of this treatment approach. We found that patients' conditions improved with LIPUS (e.g., from DLB to LBD, from PDD to PD, and from DLB to mild cognitive impairment (MCI)). In addition, LIPUS stimulation of the frontal and temporal areas in PDD patients resulted in improved motor function. Future studies should examine the effects of this treatment on cognitive function in a larger number of ATD patients. Furthermore, there is a need for detailed analyses of the results found in the PDD group using a tool such as the Hoehn & Yahr staging scale. Additionally, the unchanged cognitive functioning found in patients with MCI should be further studied. There is a need for more development of new treatment strategies for dementia given its significant impact on patients, their families, and society in general.

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Compliance with ethical standards

Ethical approval: All procedures performed in this study were in accordance with the ethical standards of the ethics committee of the Folkmore Medical Corporation Clinic Ian Center Minami according to the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent: Each participant and/or caregiver provided informed consent prior to the study.

Conflict of interest: The authors declare that they have no conflict of interest.

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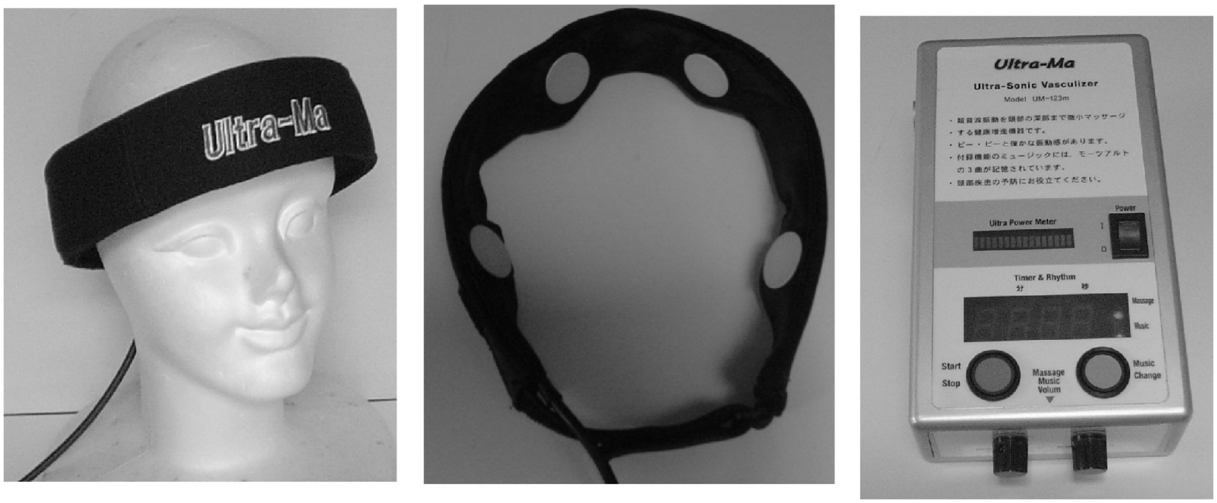


A B C

Figure 1. Low-intensity, low-frequency pulsed ultrasonic device. A. Depiction of how the transducer headband was worn by participants. B. The position of the ultrasound transducers in the headband (Type B). C. Transduction control device

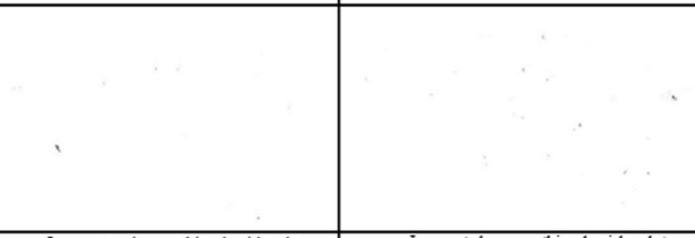
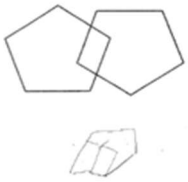
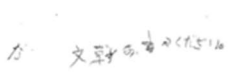
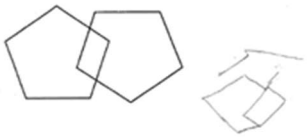
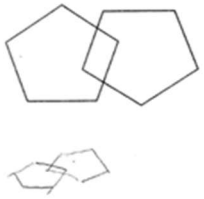
Clinical course	MMSE (1) Please write something here.	MMSE (2) Please copy the figure here.
0 w		
	I cannot write anything besides dots.	I cannot draw anything besides dots.
8 w		
	I ... am motivated to write.	I am motivated to draw.
12 w		
	It shows motivation to write,	I could draw one of the pentagons.
20 w		
	It's hawt (i.e, it is hot).	I could copy the overlapping pentagons accurately.

Figure 2. Spontaneous writing and graphic reproductions from the Mini-Mental State Examination (MMSE) (from Patient PDD-3).

The patient could not write any statement at the beginning of the LIPUS treatment session, but after sometime was able to write statements (left) and descriptions for each drawing (right).

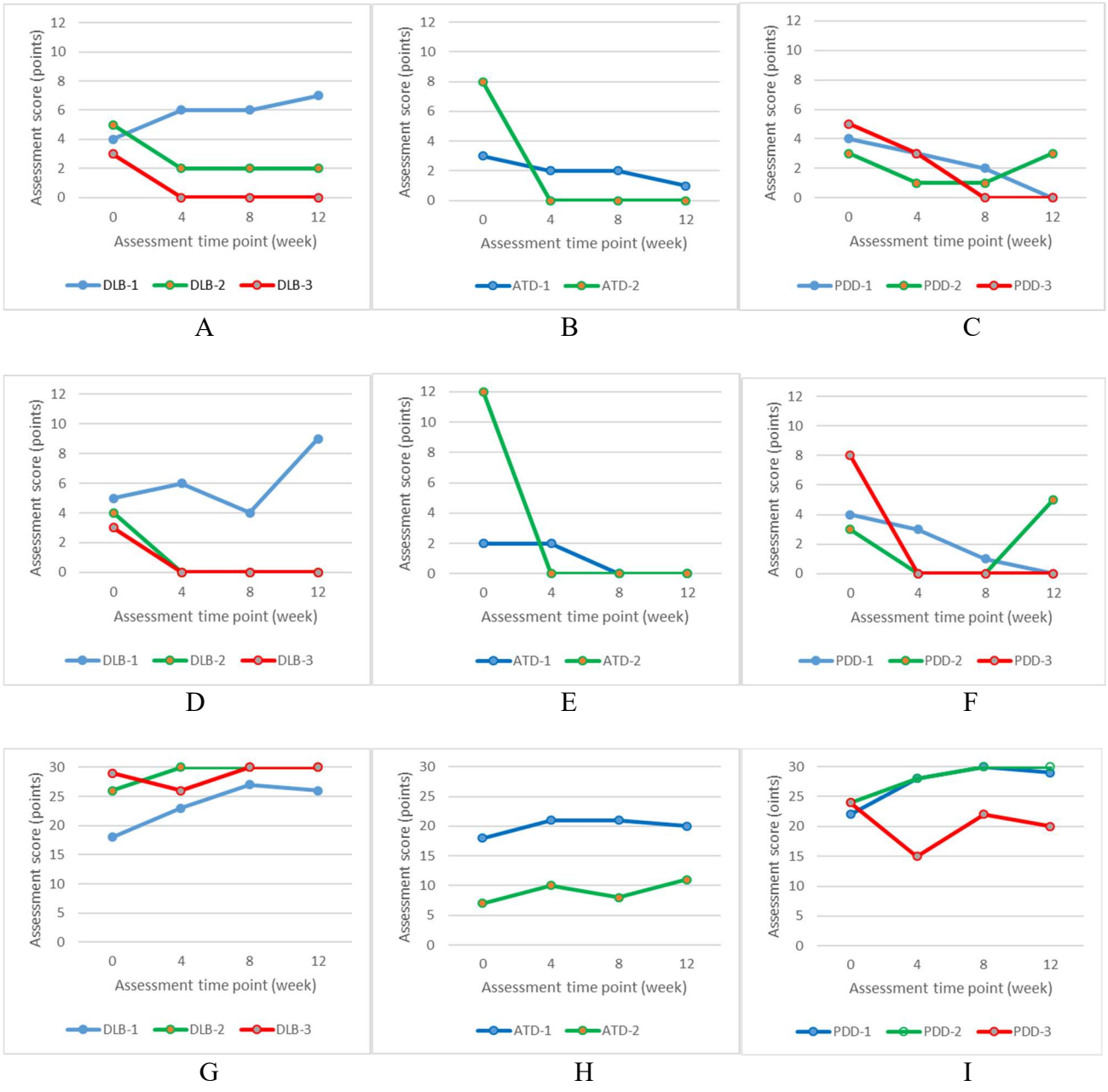


Figure 3. Neuropsychiatric Inventory Questionnaire (NPI-Q) scores across each group of patients, describing changes in patient symptom severity, caregiver burden, and Mini-Mental State Examination (MMSE) cognitive function for each patient. NPI-Q severity for A. Dementia with Lewy bodies (DLB), B. Alzheimer's type dementia (ATD) and C. Parkinson's Disease with dementia (PDD). NPI-Q burden for D. DLB, E. ATD, and F. PDD. MMSE cognitive function for G. DLB, H. ATD, and I. PDD.

Table 1. Patient data.

●: Presence of severe or frequent symptoms, ▲: Presence of symptoms, ◎: Remarkable improvement in symptoms, ○: Slight improvement in symptoms, ±: No significant changes in symptoms, ⤵: Worsening of symptoms, ?: Unknown whether there were significant changes in symptoms.

Group	Group 1			Group 2		Group 3		
Patient	DLB-1	DLB-2	DLB-3	ATD-1	ATD-2	PDD-1	PDD-2	PDD-3
Age, Sex	84, Female	73, Male	78, Female	83, Female	74, Male	77, Male	73, Male	69, Male
Diagnosis	DLB	DLB	DLB	ATD	ATD	PDD (DLB → PDD)	PDD (PDD → DLB)	PDD
Diagnosis age Age of onset Start our hospital visit	84 (2017) 81 2017.5	73 (2017) 61 2017.1	77 (2016) 74 2016.7	80 (2014) 80 2017.4	61 (2006) 61 2010.2	75 (2015) 68 2015.8	72 (2016) 70 2017.3	62 (2013) 57 2013.5
Symptoms (BPSD) and assessment results		REM sleep disorder ◎	REM sleep disorder ◎		Unstable sleep ±	▲ Tremor ◎	● Tremor ○	● Tremor ○
	Depression ◎	Depression ◎	Severe depression ◎	Mild depression ◎		▲Muscle rigidity ◎	●Muscle rigidity ○	●Muscle rigidity ○
	Severe Capgras syndrome ⤵	Memory impairment ◎	Cognitive changes ◎			● Akinesia/ Hypokinesia ◎	▲ Akinesia/ Hypokinesia ◎	● Akinesia/ Hypokinesia ◎
	Vertigo ◎	Severe dizziness on standing up ◎			Wandering ◎	● Postural reflex ◎	▲ Postural reflex ◎	● Postural reflex ○

	Visual hallucinations ◎	Dysosmia?			Violent language and yells ◎	Major symptoms, as related to those above		
						Mild depression ◎	Mild depression ◎	Drooling ±
						Fatigue ◎	Difficulty breathing ◎	Improved after medication use ◎
						Dyspnea ◎	No appetite ◎	
							Visual hallucinations ↘ (by medication discontinuation)	
Prescriptions	Memary 20 mg Aricept 10 mg Yokukansan extract Granule 2 packs (morning & evening)	Aricept D5 mg Yokukansankachimpihange extract granules 2.5 g (1/1)	Rivastach patch 18 mg (Restamin Kowa Cream)	Memary 10 mg Rivastach patch 18 mg	Aricept 8 mg Memary 20 mg Lunesta 3 mg ╳ 2	Menesit 10 mg ╳ 3	Amantadine 50 mg Artane 2 mg Dopacol 50 mg Tetramide 10 mg (at night)	Madopar ╳ 3 Reminyl 8 mg ╳ 2 Selbex Capsules 50 mg

Device type	Type A	Type A	Type A was used until week 4. Type B was used after week 4.	Type B

Table 2. Assessment [Neuropsychiatric Inventory Questionnaire (NPI-Q) and Mini-Mental State Examination (MMSE)] scores across all Dementia with Lewy bodies (DLB), Alzheimer's type dementia (ATD) and Parkinson's Disease with dementia (PDD) patients.
NPI-Q scores decreased in six cases (of eight), indicating improvements.
MMSE scores increased in seven cases (of eight), indicating improvements.

Patient	Assessment item and Assessment week	NPI-Q				Amount of changes	Special Notices	MMSE				Amount of changes
		0 w	4 w	8 w	12 w	12 w-0 w		0 w	4 w	8 w	12 w	12 w-0 w
DLB-1	Severity	4	6	6	7	3	Although depression and visual hallucinations improved, caregiver burden was high due to severe Capgras delusion.	18	23	27	26	8
	Burden	5	6	4	9	4						
DLB-2	Severity	5	2	2	2	-3		26	30	30	30	4
	Burden	4	0	0	0	-4						
DLB-3	Severity	3	0	0	0	-3		29	26	30	30	1
	Burden	3	0	0	0	-3						

ATD-1	Severity	3	2	2	1	-2		18	21	21	20	2
	Burden	2	2	0	0	-2						
ATD-2	Severity	8	0	0	0	-8	Able to sleep without taking sleeping medications. Conversation skills improved. Able to have a calm conversation.	7	10	8	11	4
	Burden	12	0	0	0	-12						
PDD-1	Severity	4	3	2	0	-4		22	28	30	29	7
	Burden	4	3	1	0	-4						
PDD-2	Severity	3	1	1	3	0	Discontinuation of Artane tablets induced frequent visual hallucinations.	24	28	30	30	6
	Burden	3	0	0	5	2						
PDD-3	Severity	5	3	0	0	-5	Parkinson's disease severity decreased.	24	15	22	20	-4
	Burden	8	0	0	0	-8						