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Clinical Utility and Safety of an Ultrasonic Head Stimulator in Dementia With Lewy Bodies

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Background: The potential of Ultra-Ma, an ultrasonic head stimulator, for the supplementary treatment of dementia with Lewy bodies (DLB) was evaluated in patients with various symptoms under poor control by drug therapy.

Methods: Patients with DLB treated with choline esterase inhibitor or L-DOPA, either alone or in combination, and who met inclusion criteria were enrolled. Four weeks of placebo stimulation was followed by 8 weeks of active ultrasonic stimulation and a 4-week follow-up. Primary endpoints were the effects of ultrasonic head stimulation on both cognitive dysfunction and behavioral and psychological symptoms of dementia (BPSD). Cognitive dysfunction was evaluated using the Japanese versions of the Mini-Mental State Examination and Montreal Cognitive Assessment, and BPSD was assessed using the Neuropsychiatric Inventory Brief Questionnaire Form. For cognitive fluctuations, the Cognitive Fluctuation Inventory served as an index. Improvements in parkinsonism, activities of daily living, and caregiver burden were examined as secondary endpoints.

Results: Twelve patients were enrolled. The primary endpoint was significantly improved during the active stimulation period, as were secondary endpoint ratings for parkinsonism and caregiver burden. No notable adverse events occurred.

Conclusions: The findings suggest that ultrasonic head stimulation has supplementary potential when combined with drug treatment in DLB.

Key Words: dementia with Lewy bodies, Parkinson disease, ultrasound, ultrasonic head stimulation, cognitive dysfunction

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Dementia with Lewy bodies (DLB) is a Lewy body disease[1] that has neuropathological continuity to Parkinson disease (PD).[2] Published treatment guidelines for DLB recommend L-DOPA for the treatment of parkinsonism and choline esterase inhibitors for the treatment of cognitive dysfunction as well as some cases of behavioral and psychological symptoms with dementia (BPSD).[1] However, treatment continuation is difficult in many cases because the pharmacological profiles of these treatments can exacerbate the respective target symptoms. Modified electroconvulsive therapy has been reported to provide useful neuromodulation for intractable cases of depression, visual hallucinations, and delusion.[3] In addition, device-aided therapies, such as deep brain stimulation, transcutaneous electrical stimulation, and enteral solutions containing L-DOPA and carbidopa, are already in clinical application for parkinsonism in PD.

Ultrasound has been reported to have neuromodulatory potential in neurodegenerative diseases;[4,5] for example, transcranial-focused ultrasound reportedly ameliorates cognitive and motor dysfunctions in Alzheimer disease and PD.[6] On the basis of these findings, percutaneous ultrasonic stimulation of the skull using Ultra-Ma (development code KMY-01, Kamiyama Mfg. Co., Ltd., https://www.worldbrain.jp/) (Supplemental Fig. 1, Supplemental Digital Content 1, http://links.lww.com/WAD/A512) was considered to be possibly neuromodulatory in the treatment of neurodegenerative dementia. Ultra-Ma is an ultrasonic head stimulator that has been developed and marketed as a healthcare device by Kamiyama Mfg. Co., Ltd., a venture business that is authorized to manufacture and market medical devices by the Ministry of Health, Labour and Welfare, Japan. We therefore conducted a pilot study on the neuromodulatory potential of this device in patients with DLB to determine whether ultrasonic head stimulation can serve as a supplement to drug treatment in patients with DLB whose symptoms are poorly controlled by drug therapy.

METHODS

Patients who were diagnosed with DLB using the revised DLB Clinical Practice Criteria and treated with choline esterase inhibitor or L-DOPA, either alone or in combination, and who did not meet any of the exclusion criteria were enrolled. Four weeks of placebo stimulation was followed by 8 weeks of active ultrasonic stimulation and a 4-week follow-up period. This was an open-label, single-arm study with a run-in placebo period. Primary endpoints were the effects of ultrasonic head stimulation on both cognitive dysfunction and BPSD. Improvements in parkinsonism, activities of daily living (ADL), and caregiver burden were evaluated as secondary endpoints. In this study, assessment tools developed and used in various

clinical studies as assessment instruments for each of the relevant conditions and symptoms were used. The scores obtained at weeks 4, 8, 12, and 16 were compared with those obtained at baseline (week 0).

This study was conducted in compliance with the Declaration of Helsinki (as revised in 2013) and the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects. It was approved by the Toranomon Hospital review board (certified by the Minister of Health, Labour and Welfare) as required by Japan's Clinical Trial Act (approval No. CRB3200008). Written informed consent to participate in the study was obtained from all participants and their caregivers.

Primary Endpoints

The presence or absence of utility of the device for cognitive dysfunction (including cognitive fluctuations) and BPSD in DLB was set as the primary endpoint. Cognitive dysfunction was evaluated using the Japanese versions of the Mini-Mental State Examination (MMSE-J) and Montreal Cognitive Assessment (MoCA-J),[7] and BPSD severity was rated using the Neuropsychiatric Inventory Brief Questionnaire Form (NPI-Q).[8,9] For cognitive fluctuations, the Cognitive Fluctuation Inventory (CFI)[10] served as an index.

Secondary Endpoints

The amelioration of parkinsonism in DLB, ADL in patients, and caregiver burden were set as the secondary endpoints. Parkinsonism was evaluated using the Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS) Part III scores,[11] ADL were assessed using the Barthel Index[12] (an index that represents physical abilities and ADL), and caregiver burden was evaluated using NPI-Q distress scores[8,9] and the Japanese short version of the Zarit Caregiver Burden Interview (J-Zarit-8).[13,14]

Participants

Patients were eligible if they were diagnosed as having DLB as evidenced by ^{123}I-metaiodobenzylguanidine myocardial scintigraphy and/or ^{123}I-ioflupane single-photon emission computerized tomography according to the criteria for the clinical diagnosis of DLB that was established by the Consortium on DLB in 2017.[1] Patients who consented to participate in this clinical study were selected as study subjects. On the basis of published results from a clinical study by Fujii et al,[15] we assumed a difference of 40% in NPI-Q score improvement rates between actual and placebo stimulations. A required sample size of ~16 to 18 patients was therefore estimated by a binomial test, with a significance level of 1% to 5% and a test power of 80% to 90%. Accordingly, the target sample size was set at 20 patients with an expected dropout rate of 10%. The study period was from June 4, 2019, to November 18, 2020.

Inclusion Criteria

Of patients diagnosed with DLB, those who met all of the following criteria were included: age 60 to 90 years, Hachinski cerebral ischemia score $\leq$4 points,[16] Japanese version of the Clinical Dementia Rating score $\geq$0.5 points,[17] a diagnosis of mild cognitive disorder and dementia, MMSE-J score 11 to 27 points, any NPI-Q severity item $\geq$1 point,[8,9] cared for by the same caregiver for not less than two-thirds of all active hours, and the patient or caregiver was able to keep a symptom diary. Furthermore, patients need to have been treated with choline esterase inhibitors, L-DOPA, or both for $\geq$4 weeks before the study initiation.

Exclusion Criteria

The following patients were excluded: patients with any other dementia diseases; patients with any substantial nervous or psychiatric diseases (eg, cerebrovascular disorders, brain tumors, schizophrenia, epilepsy, intellectual disability, head trauma with loss of consciousness, or history of brain surgery with residual defects); patients unable to undergo the required evaluations (eg, MMSE-J or NPI-Q); patients with no caregiver; patients living in a facility not attended by any dedicated caregiver; patients with an implantable medical electric device that was susceptible to electromagnetic disorder; patients with a metal coil (or similar) implanted in the cranium; patients with in-the-ear hearing aids, artificial inner ears, or implanted hearing aids; and patients considered by the investigator to be ineligible as study subjects.

Clinical Research Device

Ultra-Ma is an ultrasonic head stimulator that is currently being marketed as a healthcare device in Japan. Its specifications for an acoustic oscillator include a frequency of 30 kHz and an oscillator disc of acrylonitrile-butadiene-styrene resin 28 mm in diameter. This frequency falls outside the human audible range, so participants did not perceive the stimulus. It produces a conical distribution of acoustic intensity in the water on the oscillator disc, with a maximum output of 1.6 mW/cm^2 at the center of the oscillator surface and an average output of 0.71 mW/cm^2 on the radiation surface. The effective radiation output per oscillator can be calculated as ~4.4 mW as the product of the average output and radiation area. In the present study, head stimulation was performed at maximum intensity.

On the day on which informed consent was obtained, instructions on how to operate the device were provided by the clinical study secretariat officer, and the device was lent to the subject. The device was brought to the study site by the patient at each observation time, and the secretariat officer checked the device for any malfunctions. The secretariat officer also checked the counter to monitor the frequency of use, to determine whether the device was used as specified.

A massage band supplying weak ultrasound to the head was connected to the main body of the device via the No. 1 output terminal jack during placebo stimulation and via the No. 2 output terminal jack during active stimulation (Supplemental Fig. 1, Supplemental Digital Content 1, http://links.lww.com/WAD/A512). These connection changes were made by the secretariat officer to avoid any device operation errors by the patients or caregivers.

Procedures

A screening period started 4 weeks before the study initiation to fix the oral doses of limited concomitant medications. The limited concomitant medications consisted of choline esterase inhibitors, L-DOPA, dopamine receptor agonists, the Kampo formulations yokukansan and yokukansankachimpihange, typical and atypical antipsychotics, sleep inducers, anti-anxiety drugs, anti-epileptic drugs, and central and peripheral muscle relaxants. The new administration of these drugs was prohibited between the start of the screening period and the end of the clinical study period,

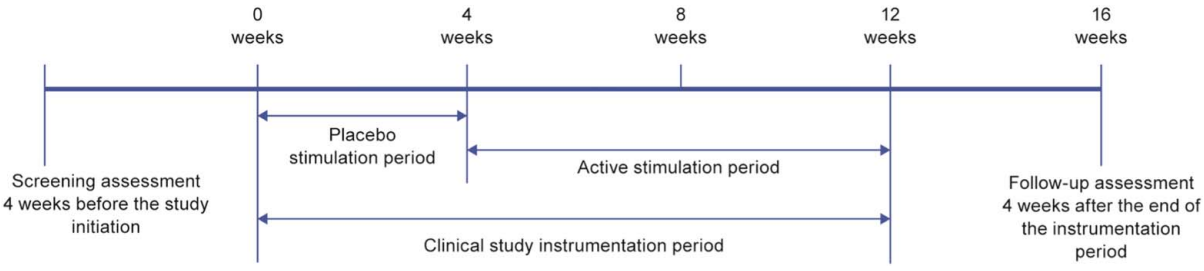

FIGURE 1. Study schedule.

and regimen changes were also prohibited for any oral medications that were being administered. If these drugs were newly administered for unavoidable reasons or if their regimens were changed, patients were excluded from the study.

The clinical study instrumentation period lasted for 12 weeks. The first 4 weeks from the study initiation were defined as the placebo stimulation period, and the subsequent 8 weeks were defined as the active stimulation period. Patients underwent ultrasonic stimulation using the ultrasonic head stimulator for 20 minutes per session, twice daily (session 1 at 10:00 AM ± 2 h; session 2 at 3:00 PM ± 2 h). There was also a follow-up period 4 weeks after the end of the instrumentation period. The study schedule is shown in Figure 1. Moreover, to check for deviations from the prescribed conditions and the occurrence of adverse events, caregivers were given a behavioral observation sheet and asked to note the time they had the patient wear the device as well as any other observations. This sheet was submitted at each evaluation time point.

The primary endpoint indices (MMSE-J, MoCA-J, NPI-Q severity, and CFI) and secondary endpoint indices (MDS-UPDRS Part III, Barthel Index, NPI-Q burden, and J-Zarit-8) were evaluated at the time of study initiation (week 0), at the end of the placebo stimulation period (week 4), at 4 weeks after the start of active stimulation (week 8), at the end of active stimulation (week 12), and at the time of follow-up (week 16), and the changes were statistically assessed.

For safety assessments, an adverse event interview, sphygmomanometry, and pulse rate measurement were performed at each evaluation time point; furthermore, blood biochemistry and electrocardiography were performed during the screening period and at the end of the clinical study instrumentation period (week 12). Behavioral observation sheets (submitted by caregivers) were also checked to ensure that no other adverse events had occurred. When participants reported adverse events, they were noted on the adverse event report form.

Statistical Analysis

We tabulated the results of all evaluation indicators obtained on the day of the start of use of the actual stimulator, at weeks 8 and 12 (± 2 d) after the start of use of the clinical study equipment, and at week 4 of the follow-up survey (± 2 d). The percentage changes between sham and actual stimulations were calculated. Moreover, descriptive statistics (number of subjects, means, SD, medians, maximums, minimums, 95% CIs) of the scores were calculated.

Intrapatient data were analyzed using the Wilcoxon signed-rank test and the paired *t* test.

To ensure accuracy and reliability, all statistical analyses were conducted by ACCERISE, Inc.

RESULTS

Twelve patients who met the inclusion criteria and provided informed consent were enrolled in the study. Initially, a sample size of 20 patients was planned; however, fewer patients were enrolled because of the worldwide COVID-19 pandemic. We therefore performed an interim analysis to verify the appropriateness of continuing the study with a number of patients that were lower than the target sample size. The scientific rationale was verified with 12 patients in the full analysis set. Table 1 shows the demographic and clinical data of the study participants.

The results for the primary and secondary endpoints are described in separate sections below. Evaluations of the behavioral observation sheet entries and equipment use frequency counters revealed that no cases deviated from the study regulations.

Primary Endpoints

Cognitive Dysfunction

MMSE-J scores were not significantly different between week 0 (17.8 ± 4.41) and the end of the placebo stimulation period (18.1 ± 4.42; $P = 0.6592$). The score at week 8 (during the active stimulation period) was 19.7 ± 4.87, showing a significant improvement compared with baseline ($P = 0.0254$). Thereafter, scores were 17.8 ± 5.62 ($P = 0.9922$) at week 12 and 17.2 ± 6.46 ($P = 0.7197$) at follow-up, showing no significant improvements compared with baseline (Table 2, Supplemental

TABLE 1. Demographic and Clinical Data of Participants

Number of cases	12 (FAS: 12)
Sex	Male: 4 (33.3%)
	Female: 8 (66.7%)
Age (y)	81.4 ± 3.60
Duration of illness (y)	2.7 ± 1.21
Residence status	Home: 10
	Nursing home: 2
Activities of daily living	Walking unaided: 10
	Walking with assistance: 1
	Using a wheelchair: 1
MMSE-J	17.8 ± 4.41
MoCA-J	12.0 ± 4.31
CFI	5.1 ± 3.53
NPI-Q severity	9.4 ± 5.42

CFI indicates Cognitive Fluctuation Inventory; FAS, full analysis set; MMSE-J, Japanese version of the Mini-Mental State Examination; MoCA-J, Japanese version of the Montreal Cognitive Assessment; NPI-Q, Neuropsychiatric Inventory Brief Questionnaire Form.

TABLE 2. Changes in Primary Endpoints

	0 wk	4 wk	8 wk	12 wk	16 wk
MMSE-J	17.8 ± 4.41	18.1 ± 4.42	19.7 ± 4.87	17.8 ± 5.62	17.2 ± 6.46
	NA	$P = 0.6592$	$*P = 0.0254$	$P = 0.9922$	$P = 0.7197$
MoCA-J	12.0 ± 4.31	12.7 ± 4.03	12.6 ± 4.58	11.8 ± 5.15	11.7 ± 4.10
	NA	$P = 0.4368$	$P = 0.3233$	$P = 0.7141$	$P = 0.6615$
NPI-Q severity	9.4 ± 5.42	7.8 ± 6.37	6.1 ± 6.29	5.8 ± 6.83	6.9 ± 6.04
	NA	$P = 0.1470$	$*P = 0.0449$	$*P = 0.0449$	$P = 0.0527$
CFI	5.1 ± 3.53	3.2 ± 3.13	2.8 ± 2.53	1.9 ± 2.31	2.3 ± 2.86
	NA	$P = 0.1289$	$P = 0.0918$	$**P = 0.0039$	$*P = 0.0234$

$*P < 0.05$.
$**P < 0.01$ vs. baseline; paired t test.
CFI indicates Cognitive Fluctuation Inventory; MMSE-J, Japanese version of the Mini-Mental State Examination; MoCA-J, Japanese version of the Montreal Cognitive Assessment; NA, not applicable; NPI-Q, Neuropsychiatric Inventory Brief Questionnaire Form.

Fig. 2, Supplemental Digital Content 1, http://links.lww.com/WAD/A512).

The MoCA-J scores showed no changes over time; scores were 12.0 ± 4.31 at week 0, 12.7 ± 4.03 ($P = 0.4368$) at week 4, 12.6 ± 4.58 ($P = 0.3233$) at week 8, 11.8 ± 5.15 ($P = 0.7141$) at week 12, and 11.7 ± 4.10 ($P = 0.6615$) at follow-up (Table 2).

CFI scores did not change significantly between week 0 (5.1 ± 3.53) and the end of the placebo stimulation period (3.2 ± 3.13; $P = 0.1289$). The score at week 12 was 1.9 ± 2.31, showing a significant improvement compared with the baseline ($P = 0.0039$). This significant improvement was retained at follow-up (2.3 ± 2.86; $P = 0.0234$) (Table 2, Supplemental Fig. 3, Supplemental Digital Content 1, http://links.lww.com/WAD/A512).

BPSD

NPI-Q severity scores did not significantly change between week 0 (9.4 ± 5.42) and the end of the placebo stimulation period (7.8 ± 6.37; $P = 0.1470$). Scores were significantly improved at week 8 (6.1 ± 6.29; $P = 0.0449$) and week 12 (5.8 ± 6.83; $P = 0.0449$), during the active stimulation period. The score at follow-up was 6.9 ± 6.04, which was not significantly different from the baseline ($P = 0.0527$) (Table 2, Supplemental Fig. 4, Supplemental Digital Content 1, http://links.lww.com/WAD/A512).

For NPI-Q severity, the total scores of the 12 sub-items were compared with the baseline in terms of changes. For convenience, changes were classified by the author according to the total score change, as follows: a reduction of ≥6 points was "markedly improved", a reduction of 4 to 5 points was "improved", a reduction of 2–3 points was "slightly improved", a reduction of 1 point to an increase of 1 point was "unchanged", an increase of 2 to 3 points was "slightly worsened", an increase of 4–5 points was "worsened", and an increase of ≥6 points was "markedly worsened". The changes during the active stimulation period were significantly improved compared with the placebo stimulation period ($P = 0.03125$) (Table 3).

Secondary Endpoints

Parkinsonism

Parkinsonism was noted in 7 of the 12 patients. The MDS-UPDRS Part III score was not significantly different between week 0 (10.4 ± 9.89) and the end of the placebo stimulation period (10.3 ± 9.08; $P = 0.8438$). The score at week 12 was 6.4 ± 5.57, showing a significant improvement compared with the baseline ($P = 0.0176$). The score at follow-up was 8.3 ± 7.19, showing no significant changes compared with the baseline ($P = 0.1230$) (Table 4, Supplemental Fig. 5A, Supplemental Digital Content 1, http://links.lww.com/WAD/A512). An analysis of motor symptoms as a sub-item revealed a significant improvement in pronation-supination movements of the hands at week 12 compared with the baseline ($P = 0.0313$) (Supplemental Fig. 5B, Supplemental Digital Content 1, http://links.lww.com/WAD/A512).

ADL

Barthel Index scores were 82.5 ± 19.48 at week 0, 85.0 ± 21.11 ($P = 0.4962$) at week 4, 86.7 ± 18.26 ($P = 0.1747$) at week 8, 85.4 ± 17.90 ($P = 0.3912$) at week 12, and 86.3 ± 17.85 ($P = 0.4428$) at the follow-up, showing no significant changes over time (Table 4, Supplemental Fig. 6, Supplemental Digital Content 1, http://links.lww.com/WAD/A512).

Caregiver Burden

NPI-Q distress scores and J-Zarit-8 scores at week 0 were 9.0 ± 7.54 and 7.3 ± 5.93, respectively. At the end of the placebo stimulation period, the scores were not significantly different from the baseline (6.4 ± 7.15, $P = 0.0859$ and 6.2 ± 4.49, $P = 0.4738$, respectively). At week 12, the scores were significantly improved compared with the baseline (4.7 ± 7.11, $P = 0.0117$ and 4.2 ± 4.30, $P = 0.0082$,

TABLE 3. Degree of Change in NPI-Q Severity

NPI-Q Severity: degree of change	Markedly improved	Improved	Slightly improved	Unchanged	Slightly worsened	Worsened	Markedly worsened
Placebo	1 (8.3%)	3 (25.0%)	3 (25.0%)	1 (8.3%)	2 (16.7%)	2 (16.7%)	0 (0.0%)
Active stimulation	4 (33.3%)	1 (8.3%)	1 (8.3%)	3 (25.0%)	1 (8.3%)	1 (8.3%)	0 (0.0%)

NPI-Q indicates Neuropsychiatric Inventory Brief Questionnaire Form.

TABLE 4. Changes in Secondary Endpoints

	0 wk	4 wk	8 wk	12 wk	16 wk
MDS-UPDRS part III	10.4 ± 9.89	10.3 ± 9.08	7.8 ± 6.34	6.4 ± 5.57	8.3 ± 7.19
	NA	$P = 0.8438$	$P = 0.0703$	*$P = 0.0176$	$P = 0.1230$
NPI-Q distress	9.0 ± 7.54	6.4 ± 7.15	4.9 ± 7.96	4.7 ± 7.11	6.1 ± 8.93
	NA	$P = 0.0859$	$P = 0.0576$	*$P = 0.0117$	$P = 0.1816$
J-Zarit-8	7.3 ± 5.93	6.2 ± 4.49	4.7 ± 4.68	4.2 ± 4.30	3.8 ± 4.77
	NA	$P = 0.4738$	$P = 0.1295$	**$P = 0.0082$	*$P = 0.0403$
Barthel index	82.5 ± 19.48	85.0 ± 21.11	86.7 ± 18.26	85.4 ± 17.90	86.3 ± 17.85
	NA	$P = 0.4962$	$P = 0.1747$	$P = 0.3912$	$P = 0.4428$

*$P < 0.05$.
**$P < 0.01$ vs. baseline; paired t test.
J-Zarit-8 indicates a Japanese short version of the Zarit Caregiver Burden Interview; MDS-UPDRS, Movement Disorder Society Unified Parkinson Disease Rating Scale; NA, not applicable; NPI-Q, Neuropsychiatric Inventory Brief Questionnaire Form.

respectively). Moreover, for J-Zarit-8, this significant improvement was retained at follow-up (3.8 ± 4.77; $P = 0.0403$) (Table 4, Supplemental Figs. 7 and 8, Supplemental Digital Content 1, http://links.lww.com/WAD/A512).

Adverse Events

At each evaluation time point, patients were questioned about contact dermatitis, other localized skin disorders, and headaches; they also received a sphygmomanometry and a pulse measurement. Behavioral observation sheets submitted by caregivers were also checked to ensure that no other adverse events had occurred. No adverse events were noted. In addition, blood biochemistry and electrocardiography were performed during the screening period and at the end of the clinical study instrumentation period (week 12), and no clinically significant change suggestive of any association with the study device was identified.

DISCUSSION

Here, we determined whether ultrasonic head stimulation served as a supplementary treatment in patients with DLB whose symptoms were poorly controlled by drug therapy, and served as a neuromodulatory treatment of DLB. The primary endpoints were improvements in cognitive dysfunction and BPSD. Primary endpoint scores improved significantly during the active stimulation period, suggesting that the ultrasonic head stimulator had a beneficial effect, especially in terms of BPSD. In the secondary endpoint of parkinsonism, MDS-UPDRS Part III scores improved significantly during the active stimulation period. Thus, ultrasonic head stimulation may be somewhat effective in ameliorating parkinsonism in DLB. Although an apparent worsening of parkinsonism is observed with fluctuating cognitive function in some cases of DLB, there was no correlation between MDS-UPDRS Part III and CFI at weeks 4 and 12.

Although the small number of cases in the present study precludes the formation of any strong conclusions, the amelioration of parkinsonism observed in the present study may be independent of changes in cognitive function.

Likewise, the ultrasonic head stimulator appeared to reduce caregiver burden in the present study; this may have resulted from symptom amelioration in the patients.

Except for CFI and J-Zarit-8, none of the indicators that improved significantly during active stimulation showed any improvements at follow-up. This finding indicates that the device may be considered as a supplementary treatment because its action is not persistent; it is only effective during the ultrasound treatment period.

The results from the present pilot study suggest the neuromodulatory potential of ultrasonic head stimulation in the treatment of DLB; however, its mechanism remains unknown, similar to that of other neuromodulatory treatments that are currently used in clinical settings. In psychiatry, modified electroconvulsive therapy is a treatment that ameliorates both mental and motor symptoms in DLB.[18,19] Although this effect has been attributed to increased dopamine release and metabolic turnover caused by electrical stimulation,[20] its mechanism of action remains to be clarified. Other studies have reported that, in patients with PD, transcranial direct current stimulation (tDCS) markedly ameliorates motor symptoms, and that cognitive function is influenced by tDCS of the prefrontal cortex.[21,22] Furthermore, small-current electric stimulation with tDCS promotes dopamine release in the striatum.[23] Regarding the mechanism of tDCS-induced symptom amelioration, the effects are likely attributable both to the primary effect of electric stimulation in activating the striatum and the secondary effect on the entire brain via the dopamine system.

A previous study has investigated the medical engineering background of the device by intracranial acoustometry using a gypsum phantom of the skull and a resin skull model. This previous study reported higher acoustic levels in the frontal and occipital regions of the brain than in the central region.[24] Furthermore, an N-isopropyl-p-[^{123}I] iodoamphetamine single-photon emission computed tomography study investigating cerebral blood flow changes in healthy subjects revealed increased cerebral blood flow in both brain hemispheres during device use.[25] Whole brain blood flow increased by ~15% compared with the 100% pre-stimulation level when measured with 2 oscillators placed bilaterally. Together, these basic findings indicate that ultrasonic stimulation improves cerebral blood flow, thus improving frontal lobe function. Alternatively, like the aforementioned neuromodulation with modified electroconvulsive therapy or tDCS, ultrasonic stimulation may increase dopamine release and promote metabolic turnover to ameliorate parkinsonism; however, the mechanism remains unknown. Transcranial-focused ultrasound, which is another ultrasound-based treatment, reportedly ameliorates cognitive dysfunction in patients with Alzheimer disease.[26] The proposed mechanism is as follows: ultrasonic

stimulation increases the regional cerebral metabolic rate of glucose in the superior frontal, middle cingulate, and fusiform gyri, and improves memory and executive function. Ultrasonic stimulation may therefore increase the metabolism of nerve cells in the brain, thus leading to functional improvements. In addition, Guidi et al[3] conducted a systematic review of the nonpharmacologic treatments of Lewy body disease.

This study has several limitations, as follows: this was a single-authored, preliminary, single-arm observational study without a control group, the study examined the effects of the device under drug treatment and not of the device alone, there was a short transition period from sham to active stimulation, and the sample size was smaller than originally planned because of the COVID-19 pandemic. Thus, the study has not achieved a sufficient level of evidence. Nevertheless, I have confirmed that the device is safe for DLB and may be effective for motor and psychiatric symptoms.

In conclusion, although the sample size in this pilot study was limited to just 12 cases in the full analysis set, the primary endpoints were attained, suggesting that Ultra-Ma may be useful in the treatment of DLB. However, the disease duration of all participants was ≤ 5 years (mean 2.7 ± 1.21 y), indicating a relatively early stage of progression. Therefore, different effects depending on disease duration and other factors should be considered. To confirm the utility of the device, we are currently preparing a multicenter clinical study of the Ultra-Ma ultrasonic head stimulator for the treatment of DLB.

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