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Cannabidiol supplement reduces epileptic seizures in the Japanese population: Cross-sectional study for intractable epilepsy patients

[1,2]Yuji Masataka, [2]Takeshi Sugiyama, [3]Ichiro Takumi, [4]Hitoshi Yamamoto

[1]Department of Neurology, Kumamoto Seijo Hospital, Kumamoto; [2]General incorporated association Green Zone Japan, Saitama; [3]Department of Neurosurgery and [4]Department of Pediatrics, St. Marianna University School of Medicine, Kanagawa, Japan

Abstract

Background: Despite very strict cannabis regulations in Japan, some cannabidiol (CBD) products have been legally distributed since 2013 and taken by some patients with epilepsy. However, the efficacy and safety of these non-pharmaceutical products have not been evaluated in patients with epilepsy in Japan. *Methods:* A self-administered questionnaire was sent to 38 patients with intractable epilepsy who were taking CBD. The questionnaire sought information on the patient background (sex, age), medical history (diagnosis, type of seizures), characteristics of CBD use (frequency, route of administration), and safety of CBD use (adverse events, side effects). Patients were also asked about changes in seizure frequency, intensity, and duration, effect on sleep, effect on daytime activity/vitality, increase/decrease in antiepileptic drug dosage, quality of life (QOL), and caregiver-assessed QOL. *Results:* Responses were received from 28 of 38 enrolled patients. The median CBD intake was 12.0 mg/kg/day. Nine patients (32.1%) were suspected of having an adverse event, but all events were mild and no patients discontinued CBD because of adverse events. Fifteen patients (53.6%) reported a decrease in seizure frequency. Moreover, two patients (7.1%) showed complete resolution of seizures. No significant correlation was found between the patient's diagnosis and seizure type or treatment efficacy. *Conclusions:* This is the first cross-sectional study of CBD users in Japan, suggesting that CBD may be an effective option for Asian patients with refractory epilepsy, regardless of diagnosis or seizure type.

Keywords: Cannabidiol, cannnabinoid, dronabinol, epilepsy, seizure, antiepileptic effects, Epidiolex®

INTRODUCTION

Cannabidiol (CBD) is a cannabinoid found specifically in the cannabis plant, and its chemical structure was first identified by Mechoulam *et al*. in 1963.[1,2] CBD is widely distributed as a medicinal and dietary supplement because it does not possess the psychoactive and addictive properties of Δ 9-tetrahydrocannabinol (THC), which is the main psychoactive substance in cannabis.

In the field of epilepsy, a phase II study was conducted in 1980 involving adult patients with temporal lobe epilepsy, and the results showed that in the actual drug group (n=8), seizure resolution was achieved in four patients and partial improvement was achieved in three patients.[3]

In 2018, as a result of Phase III studies[4,5], the CBD product, Epidiolex®, was approved by the U.S. Food and Drug Administration as a first-line treatment for Dravet syndrome and Lennox-Gastaut syndrome, and it is now available as a prescription drug. In 2020, the indication for Epidiolex® was expanded to include tuberous sclerosis complex (TSC) epilepsy.[6] In 2019, Epidiolex® was approved in the EU as adjunctive therapy with clobazam for Dravet syndrome and Lennox-Gastaut syndrome, and in April 2021, Epidiolex® was approved as adjunctive therapy for TSC in patients 2 years of age and older.[7]

The above-mentioned Epidiolex® clinical trials were mainly conducted in Europe and the United States, and the study participants were mainly Caucasian. Due to the strict cannabis regulations in Asia and the limited number of countries where medical marijuana can be used legally, reports on epilepsy in Mongoloid populations are limited, with only 34 cases of Dravet syndrome and Lennox-Gastaut syndrome reported by a Korean

Address correspondence to: Yuji Masataka, 20-902 Kamikajiyamachi, Chuo-ku, Kumamoto-shi, Kumamoto, Japan 860-0021. Tel: +81-90-4235-1982, email: y-masataka@greenzonejapan.com

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research team in 2020.[8]

Japan's regulatory law on cannabis, the Cannabis Control Law, was enacted in 1948 and has not been radically revised since its enactment. Buds and leaves are not permitted in the regulations but stems and seeds are permitted.[9] This is due to the fact that at the time of the law's enactment, cannabis stems and seeds were being cultivated in Japan for fiber harvesting and edible purposes.

As of 2021, cannabis regulations in Japan remain very strict. Simple possession of cannabis is punishable by up to 5 years in prison.[10] Moreover, the use of cannabis for medical purposes is prohibited. This is in contrast to opioids and stimulants, which can be licensed and prescribed for a limited number of indications.

Because of these strict restrictions, cannabis-based prescription drugs, such as Epidiolex®, are also subject to the Cannabis Control Law and not distributed in Japan at this time. However, since 2013, some CBD products have been legally distributed, and these products have also been recognized for their antiepileptic effects. In fact, in 2020, a case of drug-resistant epileptic encephalopathy was reported in which the patient's seizures disappeared after taking CBD supplements.[11] Since this report, there has been a growing interest among patients' families in Japan, and St. Marianna University of Medicine has begun to list Epidiolex® on its insurance schedule.[12] In 2020, a special research group of the Ministry of Health, Labour, and Welfare (MHLW) was established to develop a clinical trial system for cannabinoid medicines, and the research report was published.[13] In addition, inquiries from Japanese patients with intractable epilepsy about the use of CBD have led to the initiation of consultations. This has allowed us to collect data on patients with epilepsy who use CBD.

We collected basic data on the safety and efficacy of CBD supplements in patients with intractable epilepsy in Japan and conducted a cross-sectional study that aimed to determine whether CBD had antiepileptic effects in Asian populations.

METHODS

Eligibility

The principal investigator (PI) has been providing online consultations since 2018 to families of patients with intractable epilepsy who wish to use CBD. Patients with intractable epilepsy were defined as those whose primary physicians deemed it difficult to control seizures using standard treatment.

All family members of patients with intractable epilepsy who contacted the PI about taking CBD and subsequently took CBD at least once between May 1, 2020, and May 22, 2021, were included in the study.

Prior to the use of CBD, the PI sent a letter to the patient's physician including CBD supplement information. After the physician agreed to the use of CBD, the patient's family received Always Pure Organics CBD at a not-for-sale price (2.50 yen/mg). Prior to CBD initiation, side effects and other risks were explained, and consent was obtained from the patient's family members. The product was provided in powder form and individually diluted to 200 mg/mL using edible oil. This product was properly imported in accordance with the import standards for CBD products set by the MHLW. At the time of initial purchase, the distributor instructed the customer to start with 2 mg/kg/day twice a day and titrate upward by 2 mg/kg/day per week according to the number of seizures, up to a maximum of 20 mg/kg/day. Dosage adjustments were made at the discretion of the patient's family.

Survey method

An anonymous, self-administered questionnaire was created online using Google Forms (Google, Mountain View, CA, USA) and sent to the email address supplied by the patient's family. The questionnaire did not require any information that could identify the patient and was designed to be anonymous. The response period was from June 3, 2021, to June 10, 2021. The purpose of the research was explained at the beginning of the questionnaire. A question regarding consent to participation in the research was included, and only respondents who agreed to participate in the research were included in the study, thereby the requirement for obtaining informed consent was met. Those who did not agree to participate in the survey were excluded from the study.

Questions

The following 28 factors were included in the questionnaire (Table 1). The questionnaire was developed for this study by the PIs independently with items deemed necessary and sufficient after consultation with several pediatric epileptologists.

Table 1: Factors assessed in the questionnaire

Background	age, sex, weight, ADL, diagnosis, comorbidities, duration of illness, type of seizures, frequency of seizures, details of AEDs
CBD intake	continued use of CBD, route of administration, maximum daily dose, frequency of intake, duration of treatment, and reasons for discontinuation.
Safety of CBD	the presence of adverse events, specific symptoms, and severity of symptoms.
Efficacy of CBD	Changes in seizure frequency/intensity/duration, effect on sleep/daytime activity/vitality, increase/decrease in antiepileptic drugs, patient's QOL, caregiver's QOL

Abbreviations: ADL, activities of daily living; AEDs, anti-epileptic drugs; CBD, cannabidiol; QOL, quality of life

Factors related to patient background

These factors included age, sex, weight, activities of daily living, diagnosis, comorbidities, duration of illness, type of seizures, frequency of seizures before starting medication, details of antiepileptic drugs currently being used, and details of antiepileptic drugs tried so far.

Factors related to CBD intake

These factors included continued use of CBD, route of administration, maximum daily dose, frequency of intake, duration of treatment, and reasons for discontinuation.

Factors related to the safety of CBD

These factors included the presence of adverse events, specific symptoms, and severity of symptoms.

Efficacy of CBD

These factors included changes in seizure frequency, changes in seizure intensity, changes in seizure duration, effect on sleep, effect on daytime activity/vitality, increase/decrease in antiepileptic drugs, patient's quality of life (QOL), caregiver's QOL

Statistical analysis

In this questionnaire, we conducted a simple tabulation. Since the number of valid respondents was small (N=28), we used Fisher's exact probability test for testing our hypothesis. Fisher's exact test was performed using Python 3 programming language's Scipy library. The P-value for significance was set at 0.05.

Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by the Ethical Review Committee of the Japanese Society for Clinical Cannabinoid Research (approval no. 0002, approved May 31, 2021).

RESULTS

Of 38 questionnaires sent, completed questionnaires were received from 28 (73.7%) patients.

Patient background

The patient profiles are summarized in Table 2. All patients were of Asian ethnicity, 18 (64.3%) were male, and 10 (35.7%) were female. The patients' ages ranged from 0 to 28 years, with a median age of 4.5 years. Regarding the patient's daily activities, only one patient (3.6%) responded that these activities were independently performed, 11 patients (39.3%) needed some assistance, and 16 (57.1%) needed full assistance.

The most common diagnosis was West syndrome in seven patients (25.0%), followed by epilepsy associated with neonatal paralysis or hypoxic encephalopathy in four patients (14.3%), intractable epilepsy of unknown cause or diagnosis in four patients (14.3%), Lennox-Gastaut syndrome in three patients (10.7%), Ohtahara syndrome in two patients (7.1%), Aicardi syndrome in two patients (7.1%), epilepsy associated with 18 trisomy in two patients (7.1%), intractable epilepsy due to cortical dysplasia in one patient (3.6%), infantile epilepsy with mobile focal seizures in one patient (3.6%), epilepsy after encephalitis/encephalopathy in one patient (3.6%), symptomatic localization-related epilepsy in one patient (3.6%), and temporal lobe epilepsy in one patient (3.6%) (some patients had overlapping diagnoses).

The mean number of years since the onset of epilepsy was 4.0 years. The frequency of seizures before starting CBD was less than one seizure/day in seven patients (25%), 2–5 seizures/day in six (21.4%), 6–10 seizures/day in five (17.9%), and more than 11 seizures/day in 10 (35.7%).

Table 2: Key baseline characteristics of patients (N=28)

Sex	Male/Female	18 (64.3%)/10 (35.7%)
Age (years)	Mean (±1SD)/Median	7.25 (±7.50)/4.5
Body weight(kg)	Mean (±1SD)/Median	19.96 (±13.91)/16.7
ADL	Independent/Partial dependent/Total dependent	1 (3.6%)/11 (39.3%)/16 (57.1%)
Years from onset	Mean (±1SD)/Median	4.0 (±5.20)/3.0
Types of seizures	Generalized onset motor seizure/Focal onset seizure with impaired awareness/ others	20 (71.4%)/12 (42.9%)/16 (57.1%)
Frequency of seizures per day	~1/2~5/6~10/11~	7 (25.0%)/6(21.4%)/5 (17.9%)/10 (35.7%)
No. of previous AEDs	Mean (±1SD)/Median	4.68 (±3.11)/3.5
No. of concomitant AEDs	Mean (±1SD)/Median	2.71 (±1.10)/3.0

All patients are Asian.
AEDs, anti-epileptic drugs; SD, standard deviation
Others: focal aware seizure, focal impaired awareness seizure, generalized epileptic spasm, and myoclonic seizure

The mean number of antiepileptic drugs that the patients had ever used was 4.7, and the mean number of antiepileptic drugs administered when they started taking CBD was 2.7.

Details of CBD use

At the time of response, 21 patients (75.0%) were still taking CBD. All patients were taking CBD orally except for one patient who opted for a gastrostomy. Of the 21 patients taking CBD, seven had been on it for less than 3 months, four for 3–6 months, eight for 6–12 months, and two for longer periods.

Daily doses ranged from 0.6 mg/kg/day to 26.9 mg/kg/day, with a median of 12.0 mg/kg/day (two patients were excluded due to insufficient data).

Of those who stopped taking CBD (seven patients), five had been taking it for less than 6 months, and two had been taking it for between 6 months and 1 year. The reasons given for stopping CBD intake were "no effect" (five patients), "financial issues" (one patient), and "other" (one patient). There were no cases of discontinuation due to side effects.

Safety

In response to the question, "Did you experience any symptoms that you considered to be side effects of CBD?", nine patients (32.1%) answered "yes" and 19 patients (67.9%) answered "no". Symptoms recognized as side effects were "drowsiness/inactivity" in four patients (14.3%), "diarrhea" in two (7.1%), and "other" in three (10.7%). In terms of the severity of these symptoms, six patients responded that there was no need for withdrawal or reduction in medication, and three patients said that medication reduction was necessary, but their symptoms improved quickly.

Effects

Change in seizures and increase/decrease in antiepileptic drugs after starting CBD

Changes in seizures before and after administration are summarized in Figure 1. In response to the question, "What changes did you notice in your seizure frequency after taking the CBD?", two patients responded that seizures had "completely disappeared," 11 (39.3%) responded "very much improved," 11 patients (39.3%) responded "slightly improved," seven patients (25.0%) responded "no change," and six patients (21.4%) were unsure.

In response to the question, "What changes have you noticed in the intensity of your seizures as a result of taking CBD?", three patients (10.7%) answered "much improved," nine (32.1%) answered "somewhat improved," eight (28.6%) answered "no change," and eight (28.6%) answered, "don't know."

In response to the question, "What changes have you noticed in the duration of your seizures as a result of taking CBD?", three patients (10.7%) answered "much improved," six (21.4%) answered "somewhat improved," 11 (39.3%) answered "no

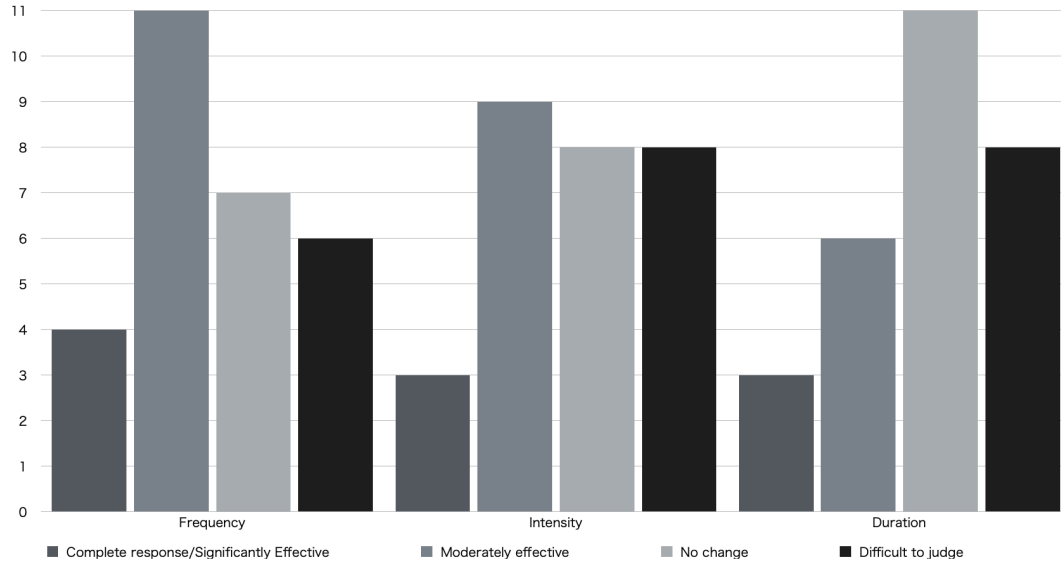

Figure 1. Responses regarding changes in seizures after initiation of cannabidiol (N=28)

change," and eight answered, "don't know."

In response to the question, "Have you increased or decreased the dose or type of other antiepileptic drugs since you started taking CBD?", eight patients (28.6%) reported that they had decreased their dosage and the other 20 patients (71.4%) answered "No change."

Secondary factors such as sleep, vitality, and quality of life

In response to the question, "How did taking CBD affect your sleep at night?", four patients (14.3%) answered "significantly improved", four (14.3%) answered "somewhat improved", 14 (50%) answered "no change", and six (21.4%) answered, "don't know". In response to the question, "How has the CBD affected your daytime activities and life?", three patients (10.7%) answered "very much improved," eight (28.6%) answered "somewhat improved," eight (28.6%) answered "no change," two (7.1%) answered "somewhat worsened," and seven (25%) answered, "don't know."

In response to the question, "How do you think the patient's quality of life has been affected?", three (10.7%) answered "very much better," 10 (35.7%) answered "somewhat better," 10 (35.7%) answered "no change," and five (17.9%) answered, "don't know." In response to the question, "How did the program affect your parents' quality of life?", four patients (14.3%) answered "much improved," 10 (35.7%) answered "somewhat improved," 11 (39.3%) answered "no change," one (3.6%) answered "worsened to some extent," and two (7.1%) said "don't know" (Figure 2).

Correlation

Dosage and side effects/seizure reduction

Of the 21 patients who continued taking CBD, two patients with missing intake data were excluded. The remaining 19 patients were divided into two groups: one with a daily intake of less than 10 mg/kg/day (low-dose group, n=6) and the other with a daily intake of more than 10 mg/kg/day (high-dose group, n=13).

The incidence rates and differences in efficacy between the two groups were then statistically compared, and the incidence of side effects was 50.0% (3/6 cases) in the low-dose group and 30.8% (4/13 cases) in the high-dose group, and the difference was not statistically significant (P=0.617).

The frequency of seizures decreased "to some extent or more" in 66.7% (4/6) of the low-dose group and 53.8% (7/13 cases) of the high-dose group, and the difference was not statistically significant (P=1.00).

Types of seizures and seizure reduction

In this questionnaire, epileptic seizures were categorized into: (1) convulsions (generalized convulsions, partial, or spreading from one part of the body to the whole body); (2) loss of consciousness (falling unconsciously or stopping

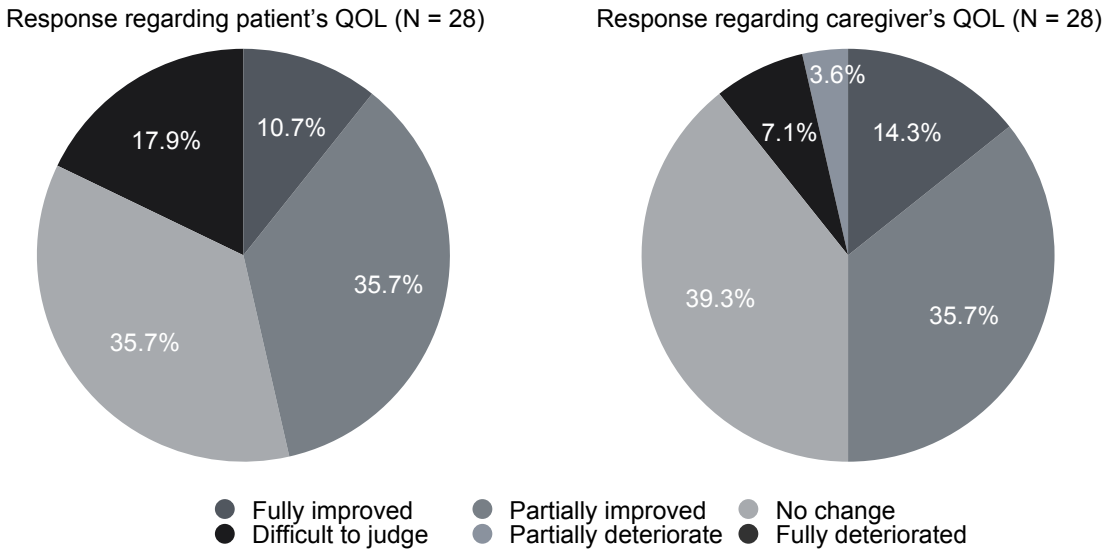

Figure 2. Responses regarding the quality of life (QOL) after initiation of cannabidiol (N=28)

movement); and (3) others (conscious but moving part of the body, body twitching, etc.) to simplify the response. The percentage of patients whose seizure frequency decreased was 50.0% (10/20 patients) for (1), 58.3% (7/12 patients) for (2), and 43.8% (7/16 patients) for (3). We also compared and verified the percentage of reduction in seizure frequency in the groups with and without each seizure type, and found no statistically significant difference in any of the seizure types. (①: P=0.69, ②: P=0.72, ③: P=0.28).

Efficacy in covered diagnosis and other diagnoses

In the US and EU, Dravet syndrome, Lennox-Gastaut syndrome, and TSC are approved by the regulatory authorities as indications for Epidiolex®, and three patients with Lennox-Gastaut syndrome were included in this study. In the group of patients with these target diseases, the seizure reduction rate was 66.7% (2/3 patients), and there was no significant difference compared with the 52.0% seizure reduction frequency (13/25 patients) in the group of patients with other diagnoses (P=1.000).

DISCUSSION

In the present study, the response rate was 73.7%. This is considered a typical value for this type of questionnaire survey. As for adverse events, "drowsiness and decreased activity" (14.2%) and "diarrhea" (7.1%), which were the most commonly reported adverse effects, were also reported in clinical trials using Epidiolex® in 21–30% and 10–15% of the actual drug groups, respectively.[5] The lower incidence of adverse events in the present study compared to the previous large-scale study can be explained by the effect of lower CBD intake. We evaluated the correlation between the dose and incidence of adverse events, considering the effect of low CBD intake on the low incidence of adverse events in this study compared with previous large-scale studies, but the results were not statistically significant. In previous studies using Epidiolex®[4,5], adverse events were mild, and no discontinuation due to adverse effects was reported in this study. These results indicate that the safety of CBD may be ensured in Asian populations.

For efficacy, patients who responded that their seizures were "completely gone," "much improved," or "somewhat improved" were defined as effective cases. In 53.6% of the patients, seizure frequency decreased, seizure intensity decreased by 42.9%, and seizure duration decreased by 32.1%. No significant correlations were found between the diagnosis or seizure type and efficacy. In a previous large study of Epidiolex® in Lennox-Gastaut syndrome, seizure frequency was reduced to 50% or less in 36% of patients in the 10 mg/kg/day group and 39% in the 20 mg/kg/day group.[5] In the present study, the efficacy rate was higher than that in the previous study, but this was because it was difficult to count the number of seizures in the present study and we had to rely on the subjective judgment of the parents. A retrospective study conducted in Korea in children with Lennox-Gastaut syndrome

and Dravet syndrome found seizure reduction in approximately 50% of patients and adverse events in 36%.[8] Of note, this is similar to the results of the present study.

There are few previous reports of studies on refractory epilepsy and CBD in Asians, and the possibility of differences in efficacy rates by race is a subject for future research.

The mechanism by which CBD suppresses epileptic seizures is still being elucidated, but it is suggested to be a novel mechanism that is structurally different from that of conventional antiepileptic drugs. Previous reports have suggested that CBD may act by modifying intracellular calcium concentrations via multiple channels, including transient receptor potential vanilloid, G protein-coupled receptor 55, and voltage-dependent anion channel.[14–16]

Aside from seizure reduction, 28.6% of the patients reported improved sleep, and 39.3% reported improved daytime activity and vigor. Sleep improvement is a major result of the use of CBD products,[17] and small clinical trials have indicated sleep improvement effects.[18] Therefore, sleep improvement in this study can be considered a direct effect of CBD. In addition, previous studies on autism spectrum disorders have shown that CBD products have a sedative effect.[19] Therefore, it is reasonable to assume that the improvement in daytime activity and vigor in this study was secondary to the reduction in seizures. A total of 46.4% of the patients felt that their QOL had improved, and 50.0% of the caregivers felt that their QOL had improved. The reason for choosing "don't know" for each item was that seven (25.0%) of the respondents had been taking the drug for less than 3 months, and it was considered difficult to judge because they were adjusting their dosage.

One limitation of this study was that the assessment of efficacy and safety was self-reported by caregivers. Most of the patients came to use CBD as a result of active information gathering, and they had high expectations. Respondents also purchased CBD at their own expense. Based on the patients' median weight (16.7 kg) and median intake (12.0 mg/kg/day), the average cost was ¥501/day. It is necessary to consider the possibility that these factors may have created cognitive bias, resulting in a higher evaluation of efficacy and safety. It is also possible that due to selection bias, the efficacy rate for patients who responded to the questionnaire was higher than the overall efficacy rate, including patients who did not respond. Furthermore, the number of cases was too small to draw any definitive conclusions. In particular, it was difficult to assess the correlation between patient background factors and CBD efficacy and safety. In addition, seven patients were included who had been taking CBD for less than three months, which may not have been long enough to determine the treatment's efficacy or safety. Despite the limitations described above, we suggest that this study may have statistical significance.

In conclusion, this was a cross-sectional survey of families of patients taking CBD supplements for intractable epilepsy in Japan, and 28 patients responded. Of all patients, 32.1% had some suspected adverse events, but the symptoms were mild, and there were no cases of discontinuation due to adverse effects. A decrease in seizure frequency was reported in 53.6% of the patients taking CBD. The results suggest that in Asian populations, CBD may be an effective option for patients with intractable epilepsy, regardless of diagnosis or seizure type.

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DISCLOSURE

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Conflict of interests: Green Zone Japan, a general incorporated association to which YM and TS belong, receives annual sponsorships of 600,000 yen from Always Pure Organics Japan Ltd.

Ethics approval: This study was approved by the Ethical Review Committee of the Japanese Society for Clinical Cannabinoid Research (approval no. 0002, approved May 31, 2021). Consent to participate was included in the patient questionnaire.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

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