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Survey Report on Parents and Patients Related to the Use of Cannabidiol Symptomatic Epilepsy Secondary to Tuberous Sclerosis Complex (TSC) in Mexico

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Authors' contributions

This work was carried out in collaboration between all authors. Author CGAV designed the study, wrote the protocol, managed the literature searches and wrote the first draft of the manuscript. Authors MPR, ELG and KLR concentrated the data of the surveys and carried out the statistical analysis of the study. All authors read and approved the final manuscript.

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ABSTRACT

A descriptive observational study using a structured survey was circulated through Facebook networks that comprised of parents of children and patients with tuberous sclerosis complex and epilepsy on conventional or medicinal cannabis/cannabidiol (CBD) treatment. Of 105 surveys, 58 were obtained by self-selection and 10 from patients treated with CBD. Forty-seven children and 11 adults, 52% male, 48% female, were included. Epileptic syndromes were present in 70.6% of the cases of which Lennox-Gastaut Syndrome (LGS) was in 20, West syndrome (WS) in 20, and epilepsy with myoclonic-astatic crises (MAE) in 6. Refractory epilepsy (RE) was present in 22 (38%) cases. Ten patients (17.2%) underwent CBD treatment; seizures decreased for 7 patients, with significant decreases in 6 and minor decreases in 1. No effect was seen in 3 patients and there were no seizure-free cases or cases where the seizure worsened. Improvement in quality of

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life parameters were observed. Mild adverse events were observed in 4 cases (40%). Monthly treatment costs ranged from $300 pesos with CBD to $35,000 pesos with everolimus. Average monthly costs with CBD were $4,039 ± 2,530 pesos. Patient and parent reports suggest medicinal cannabis is a therapeutic option offering improvement in seizures and quality of life at a moderate cost.

Keywords: Cannabidiol; tuberous sclerosis complex; epilepsy.

1. INTRODUCTION

Tuberous Sclerosis Complex (TSC) is an autosomal dominant, neurocutaneous syndrome of variable expression with multisystemic involvement. The skin, brain, eyes, kidneys, and heart are commonly affected by hamartomas, malformations, or tumor lesions. The incidence is 1 in 9,400 to 10,000 births. TSC is caused by mutations in the *TSC1 Cr9* and *TSC2 Cr16* genes that synthesize the proteins hamartine and tuberine, which act as tumor suppressors in the mTOR pathway [1]. Seizures are the most common neurological symptom of TSC, affecting about 85%, with 63% being refractory to anticonvulsants [2].

Several mechanisms have been proposed whereby medicinal cannabis (CBD) may have anticonvulsant effects [3]. The ability of CBD to block the mTOR pathway is of great interest as a new potential treatment for TSC and refractory epilepsy [4]. An extended access protocol where CBD was used as an adjunct treatment in patients with drug-resistant epilepsy secondary to TSC reported a response rate of 50% at 3 months of treatment and an average reduction of 48.8% in the frequency of seizures [5].

For several years, in Mexico and other countries, there has been an increase in the number of parents, and patients with epilepsy requesting CBD treatment, and many have already been using some of these CBD-based medicinal products [6]. Recently, legalization of medical cannabis in Mexico has given our country the opportunity to use these products as potential new treatment options for epilepsy, particularly refractory epilepsy.

The purpose of this work was to observe and document the experience of the patients' parents and patients, using medicinal cannabis (CBD) to treat epilepsy secondary to TSC in Mexico.

2. METHODOLOGY

This is a retrospective and cross-sectional observational study conducted through an online survey with the goal of documenting the experience of parents of pediatric patients and adult patients using medicinal cannabis (cannabidiol) to treat epilepsy secondary to Tuberous Sclerosis Complex (TSC) in Mexico. SurveyMonkey® Online commercial Software (www.surveymonkey.com) was used to conduct the survey and analyze the results. A license was acquired with options to develop unlimited questions, with filters of various types: open, closed, and multiple choice. Invitations to complete the survey were sent by email and/or through links via social media or to web pages. The system captures individual responses and automatically generates a report with basic statistics. The information is stored under safety standards in SuperNAP and InterNAP®. The survey was distributed over 30 days, from April 14 to May 14, 2017, to parents of children and patients in 4 Facebook groups: 1) Association Por GRACE A.C., dedicated to sharing information on the use of medicinal cannabis to treat convulsions in children, (2) Mexican Association of Tuberous Sclerosis A.C., a group of parents of pediatric patients, and adult patients with TSC, (3) Welcome to Holland, a group of parents of pediatric patients for the diffusion of medicinal cannabis in epilepsy, and (4) NPI Neurology and Integral Psychology, a private medical group page. A clause about informed consent and confidentiality for personal data was included at the start of the survey, and its acceptance was requested in order to participate. Participation was voluntary, and by self-selection.

The survey was designed to include 35 questions and 1 open opinion portion, presented in three sections: (1) personal data, (2) tuberous sclerosis information, and (3) information on epilepsy and its treatment. The invitation criteria were diagnosis of tuberous sclerosis complex and epilepsy that was currently being treated. The inclusion criteria were: (1) children, adolescents, or adults of both sexes with confirmed diagnosis of TSC according to clinical criteria and/or laboratory, imaging, genetic, or injury biopsy studies; and (2) residency in Mexico. Exclusion criteria were: (1) undiagnosed

cases of TSC and/or seizure-free, and (2) incomplete surveys. No residents outside of Mexico were included in this study.

We obtained an automated report of all the information of 105 surveys, and 58 were selected for analysis. We used the Excel® 2013 software package to obtain statistical data with central-trend measurements, absolute data, and percentages to generate tables and charts.

3. RESULTS

We analyzed 58 surveys. The age of the group of TSC patients varied from 2.4 to 29 years, with an average of 9.9 years and a standard deviation (SD) of ± 7.1 years. There was a small skew toward males (52%) in this group. Of those surveyed, 10.3% had a family history of TSC. A diagnosis of TSC was made most frequently (in 58.6%) in infants (0 to 2 years) by different methods, and various specialists and care centers; 75.8% had imaging and EEG studies performed, while 10.3% were diagnosed only based on their clinical history. Genetic confirmation by *TSC1* and *TSC2* mutation occurred in 6 cases (10.3%), and 2 cases (3.4%) were confirmed by biopsy of lesions. The general features are shown in Table 1.

There were 10 cases in which patients were treated with medicinal cannabis (cannabidiol). The most commonly used product was RSHO-X, in 6 cases, followed by artisanal products, in 2 cases, gummy CBD, in 1 case, and Nanko, in 1 case. The characteristics of the TSC group with CBD treatment are shown in Table 2.

Table 1. General characteristics of 58 cases of tuberous sclerosis and epilepsy in Mexico

Characteristic		58	%
Current age	Minimum 5 months		
	Maximum 26.0 years		
	Average: 9.9 ± 7.1 years		
	Children (0–18 years)	47	81%
	Adults (> 18 years)	11	19%
Sex	Male	30	52%
	Female	28	48%
Age of diagnosis of TSC	Minimum	RN	
	Maximum	15 years	
	Average	2.3 ± 3.3	
	Newborn	7	12.0%
	1 month–2 years	34	58.6%
	2–5 years	11	18.9%
	5–12 years	4	6.8%
	12–18 years	2	3.4%
	18–25 years	0	0%
Diagnostic methods	Medical history	6	10.3%
	Neurological studies	44	75.8%
	Genetic studies	6	10.3%
	Injury biopsy	2	3.4%
Family history of TSC	Absent	40	68.9%
	Unknown	12	20.6%
	Present	6	10.3%
	Grandparents	1	
	Parents	2	
	Brothers	3	
	Uncles	2	
	Cousins	2	
Age of onset of epilepsy	Newborn	9	10.0%
	1 month–2 years	37	60.0%
	2–5 years	4	12.0%
	5–12 years	3	10.0%
	12–18 years	3	2.0%
	18–25 years	2	6.0%
	> 25 years	0	0.0%

Characteristic		58	%
Type of seizure	Focal	3	20.7%
	Generalized	18	63.6%
	Myoclonic	7	
	Atonic	8	
	Tonic	14	
	Tonic-Clonic	22	
	Atypical absences	7	
	Infantile spasms	6	
	Mixed	37	15.5%
Epileptic syndrome	Some or several	41	70.6%
	S. Lennox-Gastaut	20	
	S. West	15	
	S. Doose	0	
	S. Ohtahara	0	
	E. Myoclonic-astatic	6	
	None	17	29.4%
Clinical diagnosis of refractory epilepsy	Yes	22	38.0%
	No	36	62.0%
Treatment received	Anticonvulsants	58	100%
	Vigabatrin	29	50%
	Steroids	6	10.3%
	Ketogenic diet	3	5.1%
	IVIG	2	3.4%
	Everolimus	6	10.3%
	ACTH	4	6.8%
	Epilepsy surgery	1	1.7%
	N.V. Stimulator	0	0%
Cannabidiol brand	RSHO-X (5000 mg)	6	60%
	Crafts (NA)	2	20%
	Nanko (300 mg)	1	10%
	Gummy CBD	1	10%

Table 2. Characteristics of TSC cases in treatment with medicinal cannabis

Case	Sex	Age years	ES	RE	Product	Dose mg/Kg/d	Time of treatment	Decrease rate	Adverse effects
1	M	2	LGS	+	RSHO-X	3.6 mg	1 m	80–100%	+
2	M	3	WS/LGS	-	GUMMIES	1.0 mg	2 m	80–100%	-
3	F	4	WS/LGS	+	Artisanal	?	12 m	80–100%	+
4	F	5	WS/LGS	+	RSHO-X	4.2 mg	12 m	80–100%	-
5	M	5	WS	+	RSHO-X	19 mg	12 m	< 25%	+
6	M	8	LGS	+	RSHO-X	1.8 mg	8 m	80–100%	-
7	F	11	LGS	+	Nanko	0.8 mg	1 m	25–50%	-
8	F	15	No	+	RSHO-X	1.75 mg	15 d	0%	-
9	M	16	No	-	Artisanal	?	13 m	80–100%	+
10	F	24	No	-	RSHO-X	0.7 mg	1 m	0%	-

ES = Epileptic syndrome, RE = Refractory Epilepsy, LGS = Lennox Gastaut Syndrome, WS= West Syndrome, ? = Unknown, + = Present, - = Absent

The results indicate a substantial decrease (80–100%) in seizures in 6 of the cases. No seizure-free or worsening cases were reported with CBD. Dosing of CBD varied from 0.7 to 19 mg/kg/day (± 4.1 mg/kg/day), although it is not possible to obtain the exact dosage for artisanal products Table 3. Four cases presented with mild adverse effects, as shown in Table 4.

Parents reported positive effects on CBD treatment on seizures and in other clinical symptoms with Cannabidiol treatment, as shown in Figs. 1 and 2.

The maximum monthly cost of anticonvulsant treatments were: $35,000 pesos for everolimus, $6,500 pesos for medicinal cannabis, and $5,000 pesos for various antiepileptic drugs in polypharmacy. The minimum expenditure was $300 pesos for medicinal cannabis in its artisanal form. Monthly spending averages for the different treatments were: $32,500 pesos for everolimus, $4,039.17 pesos for medicinal cannabis, $2,128.60 pesos for antiepileptics, $1,717.65 pesos for vigabatrin, and $1,200 pesos for steroids. No treatment expense with adrenocorticotropic hormone (ACTH) was reported. See Table 5.

Table 3. Decrease rate in seizure frequency with medicinal cannabis treatment

	% Decrease	10	%
	General	7	70%
Seizure-Free	100%	0	0%
Significant	80–100%	6	60%
Moderate	50–80%	0	0%
Slight	25–50%	1	10%
Unchanged	± 25%	3	10%
Worsening	> 25%	0	0%

4. DISCUSSION

This is the first observational study on the use of medicinal cannabis in epilepsy secondary to TSC in Mexico. We believe that the reports by parents and patients in our survey are important, as cannabidiol use in epilepsy appears to be a potential new treatment option with good efficacy and safety.

In a retrospective study of the natural history of epilepsy in patients with TSC, among 291 cases, epilepsy was found in 99.2%, with 62.5% developing refractory epilepsy [7]. Our study differs from Hess, that reported as we noted a lower rate of refractory epilepsy (38% vs. 62.5%), probably due to sub-diagnosis. We also observed a higher percentage of LGS (34.4% vs. 27.4%) in our population.

The efficacy profile of medicinal cannabis treatment in our study indicates that with more than 1 month of treatment, there was a reduction in seizures by 80%, in 60% of the cases. Additionally, there were no reports of seizure-free cases. One patient (case #5) showed no improvement, despite having the highest weighted dose of the group. No patients had aggravation of the convulsive process. In the study conducted by Hess et al. [5], a reduction rate of 50–90% in seizures was obtained in 38.8% of cases at 3 months, and 1 case was seizure-free. In this study, doses ranged from 13 to 50 mg/kg/day (± = 34.5 mg/kg/day) compared to 0.7 to 19 mg/kg/day (± = 4.1 mg/kg/day) in our previous study. In our study, previously reported CBD side effects were present in 66.7%, and included drowsiness, ataxia, and mild-intensity diarrhea. Parents in our survey reported mild adverse effects in pediatric patients in 4 cases (40%).

Table 4. Adverse effects with medicinal cannabis treatment

Case	Number	Adverse effects	Severity	Intervention
1	4	Fatigue, drowsiness, insomnia, increased appetite	Mild	No need to lower or suspend the medication, symptoms disappeared with time.
3	1	Insomnia	Mild	No need to lower or suspend treatment, symptom disappeared with time.
5	1	Drowsiness	Mild	No need to lower or suspend treatment, symptom disappeared with time.
9	1	Increased appetite	Mild	No need to lower or suspend treatment, symptom disappeared with time.

Table 5. Monthly cost, in MX pesos, of different treatments for epilepsy in TSC

	Antiepileptic	Vigabatrin	Everolimus	Steroids	Cannabis
Average	$2,128.60	$1,717.65	$32,500.00	$1,200.00	$4,039.17
Median	$2,000.00	$1,600.00	$32,500.00	$1,200.00	$5,320.00
Mode	$2,000.00	$2,000.00	#N/A	#N/A	$6,500.00
D.E.	$1,337.96	$833.28	$3,535.53	$282.84	$2,530.29
Max.	$5,000.00	$4,500.00	$35,000.00	$1,400.00	$6,500.00
Min.	$300.00	$900.00	$30,000.00	$1,000.00	$300.00

#N/A=Not applicable

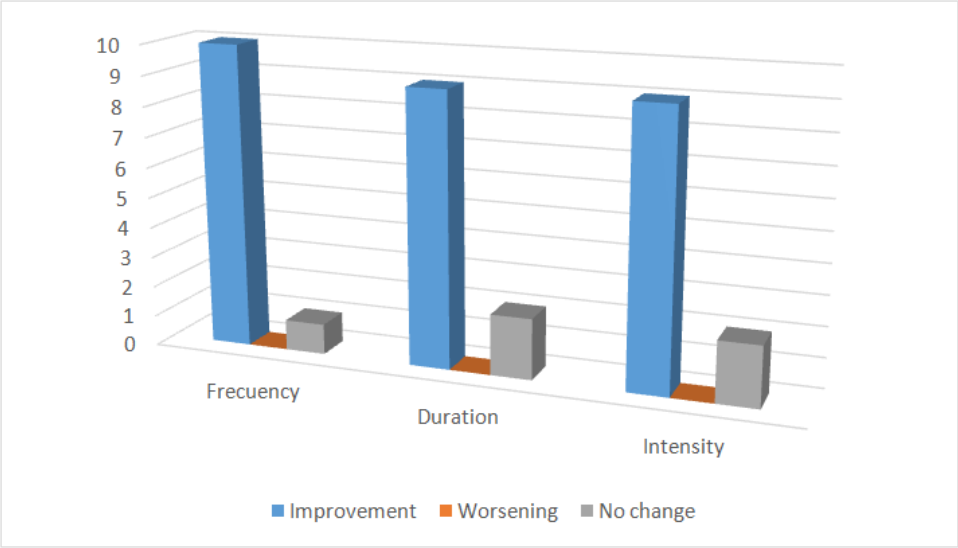

Fig. 1. Effect of treatment with cannabidiol on convulsive seizures

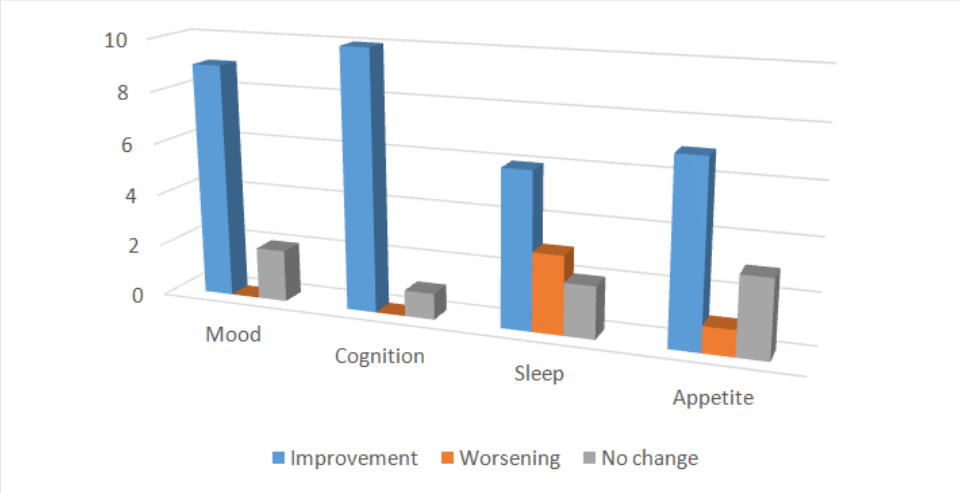

Fig. 2. Effects of cannabidiol on other clinical symptoms

We consider that the low dose administered to the patients in our study may have been the cause of the lower rate of efficacy, but fewer side effects, were seen in our study. Alternatively, this difference could be due to a variation in the response to the endocannabinoid system in Mexican patients.

The European consensus for the clinical management of epilepsy in TSC [8] recommends vigabatrin as a first line of treatment for infantile spasms, used at the minimum effective dose, and for the shortest time possible, to minimize the risk of retinal toxicity. The second line of treatment involves corticosteroids or ACTH in cases of hypsarrhythmia. If hypsarrhythmia is absent, but focal/multifocal alterations is present, topiramate may be used. The third line of treatment is a ketogenic diet or other antiepileptic drugs.

In our survey, the use of therapeutic resources is consistent with these recommendations, as the most commonly used drug is vigabatrin, followed by steroids and a ketogenic diet. In Mexico, there is no access to ACTH, which would be administered in infantile spasms with hypsarrhythmia. In the United States market, this drug is expensive (synthetic ACTH, $3,770/ month).

Everolimus [9] is a cancer treatment rapamycin analog, but has demonstrated efficacy in TSC epilepsy. Everolimus treatment results in significant improvement in 73% of cases, with 20% seizure-free, and 35% with a reduction in seizure frequency of 90%. However, the cost of this treatment is high (from $30,000 to $35,000 pesos per month in Mexico) when compared with vigabatrin ($900 to $4,500 pesos per month), steroids ($1,000 to $3,200 pesos per month) and CBD (not including artisanal, at $4,737 per month on average). Due to the relative cost and efficacy rate, vigabatrin remains a first-line choice in the treatment of TSC, but it is limited by its potential to cause retinal damage.

Vagus nerve stimulation rarely manages to completely control the seizures, but does result in a significant decrease in their frequency. In our survey, we found that there were no patients treated with vagus nerve stimulation. Surgery is indicated early in refractory epilepsy if the seizure-causing lesion can be clearly identified. Since focal injuries can lead to bilateral seizures and infantile spasms, surgery may also be considered in these cases. Only 1 patient in this survey underwent surgical treatment for epilepsy.

Medicinal cannabis can be a treatment option with a good rate of efficacy and safety [10]. Reducing its cost could make it a first or second line treatment for epilepsy secondary to TSC in the future.

Our study is limited by the small sample size and is biased by the type of survey used. Additionally, a placebo effect has been reported in up to 20% of studies of other anticonvulsants.

We believe that the rate of seizure reduction in Mexican patients can be improved by establishing a protocol for a gradual increase in CBD doses of 5 mg/kg/day per week to a maximum of 25 mg/kg/day. Between its regulatory effect on neuronal excitability, and its action as an inhibitor of the mTOR pathway, CBD presents as an exciting potential resource for the treatment of epilepsy secondary to TSC.

5. CONCLUSIONS

The experience of parents and patients with medicinal cannabis (CBD), as reported in our survey, suggests that CBD reduced the frequency, intensity, and duration of convulsive crises secondary to TSC. Additionally, the reports indicate that there was improvement in other clinical symptoms. This therapeutic resource is already available in our country, costs lesser than other treatments. More statistically solid controlled studies are required to support the use of cannabidiol (medicinal cannabis) in epilepsy secondary to TSC.

SUPPLEMENTARY MATERIAL

The supplementary data link:

https://drive.google.com/file/d/0ByGb_ZCAYvvJM3BZYW9fSE5zLW8/view

CONSENT

All authors declare that written informed consent was obtained in each survey from the patient (or other approved parties) for publication of this paper.

ETHICAL APPROVAL

It is not applicable.

FINANCING

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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