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Quality of Life of Childhood Epilepsy (QOLCE) in pediatric patients enrolled in a prospective, open-label clinical study with cannabidiol (CBD)

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Summary

Recent clinical trials indicate that cannabidiol (CBD) may reduce seizure frequency in pediatric patients with certain forms of treatment-resistant epilepsy. Many of these patients experience significant impairments in quality of life (QOL) in physical, mental, and social dimensions of health. In this study, we measured the caregiver-reported Quality of Life of Childhood Epilepsy (QOLCE) in a subset of patients enrolled in a prospective, open-label clinical study of CBD. Results from caregivers of 48 patients indicated an 8.2 ± 9.9 point improvement in overall patient QOLCE ($p<0.001$) following 12 weeks of CBD. Subscores with improvement included energy/fatigue, memory, control/helplessness, other cognitive functions, social interactions, behavior and global QOL. These differences were not correlated to changes in seizure frequency or adverse events. The results suggest that CBD may have beneficial effects on patient QOL, distinct from its seizure-reducing effects, however further studies in placebo-controlled, double-blind trials are necessary to confirm this finding.

Keywords

cannabidiol; quality of life; seizures; pediatric; epilepsy

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Introduction

Children with chronic epilepsy experience significant impairments in physical, mental, and social domains of quality of life (QOL) as reported by patients or parents [1; 2]. Epilepsy-specific QOL questionnaires can evaluate the effects of seizures and antiepileptic medications (AEDs) [3; 4], supplementing assessment by physicians who often fail to address under-reported symptoms and or do not directly address physical, psychosocial, and occupational/educational effects of epilepsy and therapies [5].

Epilepsy can contribute to low self-esteem, anxiety, depression, impaired memory and attention, lack of independence, and social stigma [1; 2; 6]. The Quality of Life in Childhood Epilepsy (QOLCE) survey measures multiple QOL domains in different populations, with good response rates, internal consistency, and test-retest reliability [1; 2; 7; 8].

An open-label trial [9] suggested that CBD can reduce seizure frequency in children and young adults with treatment-resistant epilepsy, and three randomized, placebo controlled phase III trials have been completed in Dravet and Lennox Gastaut syndromes (NCT02091375, NCT02224560, NCT02224560) and preliminary reports support efficacy in both syndromes [10]. Parents of children with severe epilepsies treated with vernacular CBD preparations reported improved mood, behavior, language, alertness, motor skills, and sleep, but also drowsiness, fatigue and reduced appetite [6; 11]. A Phase II Expanded Access Program (EAP) study found CBD was generally well-tolerated; common adverse events included somnolence (25%), decreased appetite (19%), diarrhea (19%), fatigue (13%), and convulsions (11%) [9]. Here, we directly examine the change in QOLCE in patients before and after 12 weeks of CBD treatment.

Methods

Study background and design

Patients enrolled in a prospective, physician-sponsored, open-label EAP at the NYU Epilepsy Center between Jan 15, 2014, and April 15, 2015, to measure potential seizure-reducing properties of purified CBD (Epidiolex, GW Pharmaceuticals, UK). These subjects included a subset of those previously described [9] and subjects enrolled after the reported cut-off date. Patients aged 1–30 years and had intractable childhood-onset epilepsy with four or more countable seizures with a motor component per four-week period. We excluded patients with baseline liver, renal, or hematological laboratory abnormalities, or initiation of felbamate or vigabatrin within 6 months before enrollment. Patients with progressive disorders were excluded. The NYU Langone Medical Center institutional review board approved the study, and written informed consent was obtained from the subject/legally authorized representative.

After enrollment, parents/patients kept a four-week pre-CBD baseline period during which patients were on stable doses of AEDs, dietary therapy, and/or stable vagus nerve stimulator settings. Seizure diaries reported seizures with a sustained (>3 s) motor component (motor seizures), including tonic-clonic, tonic, clonic, atonic, and focal seizures with prominent motor features. Patients received a 99% oil-based CBD extract of constant composition in a

100 mg/mL sesame oil-based solution administered orally or by gastric tube. CBD (2–5 mg/kg/day divided in twice-daily dosing) was added to the baseline AEDs, then titrated (2–5 mg/kg/week until intolerance or maximum dose of 50 mg/kg/day). Background AEDs and VNS settings were kept stable during the 12-week observation period. Single dose reductions in background AEDs were permitted if the investigator felt there was worsening sedation (attributed to pharmacokinetic or pharmacodynamics interactions with CBD); no new medications were started.

Quality of Life Assessment

Caregivers completed the U.S. versions of the Quality of Life in Childhood Epilepsy (QOLCE) survey [12] at the pre-treatment visit and after 12 weeks of treatment. The questionnaire assessed 91 items, subdivided into five domains: physical function (12 items, including physical restrictions and energy/fatigue subscales), cognitive function (23), emotional well-being (19), social function (12), and behavior (23). The QOLCE also measured general health compared to children of the same age and overall QOL. Responses scored on a five point Likert scale, and subscore values were linearly converted to a 100-point scale [8]. Overall QOL was computed by obtaining the sum of the subscores and dividing by 16. Mean imputation using the group's question responses at the same time point (baseline or post-CBD) was performed for individual missing responses as described [1; 12].

Seizure Frequency

Mean and % change in monthly motor seizure frequency were calculated for each subject [9] during the 4-week baseline period and over the 12-week observation period following CBD initiation. Responders had ≥ 50% reduction in mean monthly motor seizures from baseline.

Statistical Analysis

Descriptive statistics (Tables 1 and 2) were calculated for demographic data, seizure frequency, and QOLCE measurements. Variance was expressed as standard deviation for means and 25–75%tile interquartile range (IQR) for medians. Baseline and post-CBD treatment (12 week) total motor seizure rates were compared using a Wilcoxon Rank Sum test. Baseline and post-CBD treatment QOLCE values were compared using paired *t*-test for the overall QOL score. Post-hoc comparison of individual subscore changes were also performed using paired *t*-test with Holm-Bonferroni correction for multiple comparisons with alpha = 0.05. Secondary analyses compared QOLCE score changes between responders (≥50% reduction in total convulsive seizures) and non-responders to CBD, as well as those patients with and without particular adverse events using a 2 × 2 mixed ANOVA design (responder or adverse effect [yes vs no] × (baseline QOL score vs post-CBD QOL score). Associations between percent seizure reduction and overall percentage change in QOLCE scores were assessed via simple linear regression analysis. All analyses were conducted using the Statistical Package for Social Sciences version 22 (IBM SPSS, Armonk, NY).

Role of the funding source

GW Pharmaceuticals had no role in study design, data analysis, data interpretation, or writing of the report, or in the decision to submit the paper for publication. The corresponding author had full access to all study data and decided to submit for publication.

Results

Sixty subjects enrolled in the EAP at NYU between January 15, 2014 and April 15, 2015. One patient was excluded due to a progressive neurological disorder. Eighty percent of patient caregivers (N=48) completed both pre- and post-treatment QOLCE surveys and were included in subsequent analysis. Reasons for incomplete forms include: withdrawal of consent (N = 1), subject death from probable Sudden Unexpected Death in Epilepsy (SUDEP) (N = 1), and failure to return survey form (N = 10). Table 1 provides the baseline characteristics for 48 study subjects. There was no difference in age, number of baseline AEDs, baseline motor seizure frequency (Mann-Whitney U test, $p > 0.05$) or gender (Fisher Exact test, p=0.73) between subjects who completed the QOLCE survey and those who did not.

Changes in seizure in frequency

The median baseline monthly motor seizure frequency was 27.5 (IQR: 12.0 – 89.0) and median baseline monthly total seizure frequency was 33.0 (IQR: 16.4 – 108.7). The median dose achieved during the titration period was 25mg/kg (range: 10.2 – 51). The median monthly motor seizure frequency during the 12-week observation period was 13.9 (IQR: 5.2 – 46.4) and median percent change from baseline was −39.4% (IRQ: −69.6 – −12.0%; Z= −3.8, p<0.001). Twenty subjects (41.7%) were ≥ 50% responders. There was no significant difference in median percent change in seizure frequency between the 48 subjects who completed both QOLCE surveys and the 12 that did not (data not shown; Z=−1.2, p=0.22).

Changes in reported QOLCE

The baseline mean overall QOLCE score was 37.8 ± 7.8. Following 12 weeks of treatment, the mean QOLCE score increased to 45.7 ± 8.5 (t =5.7, p < 0.001); with a mean change from baseline of 8.1 ± 9.9. Table 2 lists domain specific QOLCE subscores. Univariate analysis adjusted for multiple comparisons identified statistically significant improvements in energy/fatigue (t = 3.1, unadjusted p=0.003), memory (t =7.1, unadjusted p < 0.001), other cognitive (t=4.2, unadjusted p<0.001), control/helplessness (t= 4.6, unadjusted p < 0.001), social interactions (t = 3.1, unadjusted p = 0.003), behavior (t=3.4, unadjusted p=0.001) and QOL item subscores (t = 4.6, p < 0.001) following 12 weeks of CBD.

Relationship of QOLCE changes, seizures and reported adverse effects

There was no relationship between change in weighted QOLCE and percent change in monthly motor seizures (β= −0.002, p = 0.9), and overall QOLCE did not differ between ≥50% responders and non-responders (mean change 6.6 ± 8.5 vs 9.0 ± 11.1, F = 0.06, p = 0.802). There was no observed relationship between the number of adverse effects and overall QOLCE score change (β= 0.07, p = 0.671). Patients that experienced somnolence, drowsiness, or fatigue (N=28 vs. N=20 without) did not differ in scores of physical

restrictions, energy/fatigue, or activity (F=0.11, p = 0.742, data not shown). Nor were there differences in the change in anxiety, depression, or behavior subscores among subjects with psychiatric adverse events (N = 10) compared to those who did not (N = 38; p > 0.05; data not shown).

Discussion

We observed improvements in caregiver-reported QOL in children and young adults with severe, childhood-onset epilepsy in a prospective, open-label study of CBD. Following CBD treatment, caregivers reported significant improvements in multiple QOLCE domains, including energy/fatigue, memory, other cognitive, control/helplessness, social interactions, and behavior, as well as improvements in general QOL subscores. These findings paralleled prior observational studies with medicinal cannabis treatment in treatment-resistant epilepsy populations; parents reported improved mood, alertness, sleep, behavior, and language [6; 11].

It is difficult to discern whether improved QOL results primarily from direct medication effects, reduced seizures, or psychological benefits of reduced seizures, as each factor independently contributes to QOL but may be causally interrelated [13]. We found no correlation between improvements in QOLCE and adverse events or changes in seizure frequency with CBD, which was surprising given the relationship between seizure frequency, medication side effects, and QOL in epilepsy [13]. Thus, CBD may improve health related QOL *independent from* its effects on reducing overall seizure burden [9]. Improvements in sleep, mood, and overall mental health may be reflect anxiolytic or other effects of CBD (reviewed in [14]).

The primary limitations of this study are lack of blinding or comparator group. Conclusions from this study should be interpreted cautiously since the patients, caregivers, and clinicians were aware they were receiving CBD, increasing the potential for placebo responses seen in retrospective trials with CBD [6]. Furthermore, caregiver-reported QOL measures may partly reflect views of the caregiver rather than patient experiences, prompting future studies measuring the QOL of caregivers alone or patients themselves. Expectations may have been heightened from media coverage and selection to participate, and other clinical trial benefits (“Hawthorne Effect”), potentially biasing parents to reported improvements. A minority of eligible caregivers (17%) did not complete both pre- and post-CBD QOLCE, which may bias our results to positive endorsements of QOL changes. In addition, we did not prospectively track other seizure-related factors such as duration of seizures or post-ictal state, and improvements in these factors could have also lead to QOL benefits independent of seizure frequency. Finally, repeated exposure to the QOLCE questionnaire may also lead to improved scores independent of treatment effect, however prior studies using repeated administration of the QOLCE scale in newly-treated [15] or surgical [12] patients did not demonstrate a significant improvement in the patients who had continued seizures. To rule out a potential CBD-independent practice effect of longitudinal improvement and prevent the aforementioned biases, we encourage future randomized double-blind clinical trials to assess QOL with of CBD in specific epilepsy syndromes.

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Table 1

Baseline characteristics of subjects completing QOLCE before and after cannabidiol (CBD) treatment (N = 48).

Median Age (Range)	11.7	(3.1 – 27.2)
N Female (%)	25	(52%)
Median baseline AEDs (range)	3	(1 – 5)
Median max dose CBD (range)	28.2	(10.2 – 51)
Baseline Median Motor Seizures per month (IQR)	27.5	(12 – 89)
Epilepsy Syndrome/Etiology	*N*	*%*
Dravet Syndrome	8	16.7
Genetic generalized epilepsy	8	16.7
Lennox-Gastaut Syndrome	8	16.7
CDKL5	6	12.5
Aicardi Syndrome	5	10.5
Duplication 15q syndromes	5	10.5
Unknown	3	6.3
Other	5	10.5

Table 2

QOLCE Scores at baseline and after 12 weeks following initiation of CBD

QOLCE Subdomain	No. Questions	Baseline Mean (SD)	Post-CBD Mean (SD)	Mean Difference (SD)	*t*-score	*p*-value*
Physical Restrictions	10	16.90 (11.18)	21.89 (11.99)	5.09 (12.66)	2.79	0.008
Energy/Fatigue	2	42.26 (20.23)	52.28 (15.20)	10.12 (22.35)	3.14	0.003**
Attention/Concentration	5	25.33 (19.43)	32.04 (16.96)	6.50 (19.24)	2.34	0.024
Memory	6	30.80 (16.19)	45.91 (12.96)	15.02 (14.70)	7.08	< 0.001**
Language	8	21.37 (12.28)	26.38 (13.53)	5.04 (13.03)	2.68	0.010
Other Cognitive	3	12.89 (17.75)	24.39 (15.37)	11.41 (19.02)	4.16	< 0.001**
Depression	4	68.80 (10.70)	72.99 (8.87)	4.27 (10.69)	2.77	0.008
Anxiety	5	63.42 (9.37)	65.15 (15.71)	1.57 (13.19)	0.77	0.446
Control/helplessness	4	49.00 (11.34)	56.07 (11.70)	7.78 (11.85)	4.55	< 0.001**
Self-esteem	5	65.94 (8.84)	67.90 (9.05)	2.24 (7.70)	2.02	0.049
Social Interactions	5	25.01 (16.54)	37.60 (26.35)	12.68 (28.33)	3.10	0.003**
Social Activities	3	27.24 (10.81)	32.12 (13.59)	4.87 (13.84)	2.44	0.019
Stigma Item	1	43.26 (27.23)	51.25 (26.85)	8.18 (32.05)	1.77	0.084
Behavior	16	50.35 (9.04)	54.30 (8.33)	4.18 (8.57)	3.38	0.001**
General health item	1	27.43 (25.17)	40.36 (28.32)	13.95 (34.19)	2.83	0.007
Quality of life item	1	35.02 (18.10)	53.80 (20.78)	19.05 (28.52)	4.63	< 0.001**
Overall QOL		37.81 (7.78)	45.74 (8.50)	8.12 (9.85)	5.71	<0.001

*unadjusted p values

**significant (corrected alpha <0.05) after Holm-Bonferroni correction for familywise error rates