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Quality of life in adults enrolled in an open-label study of cannabidiol (CBD) for treatment-resistant epilepsy

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ABSTRACT

Treatment-resistant epilepsy (TRE) is associated with low quality of life (QOL). Cannabidiol (CBD) may improve QOL, but it is unclear if such improvements are independent of improvements in seizure control. Our aim was to compare QOL at baseline and after 1 year of treatment with CBD. We hypothesized that QOL would improve independent of changes in seizure frequency (SF) or severity, mood, or adverse events. We assessed QOL using Quality of Life in Epilepsy-89 (QOLIE-89) in an open-label study of purified CBD (Epidiolex®) for the treatment of TRE. All participants received CBD, starting at 5 mg/kg/day and titrated to 50 mg/kg/day in increments of 5 mg/kg/day. We collected QOLIE-89 in adult participants at enrollment and after 1 year of treatment, or at study exit if earlier. We analyzed if the change in QOLIE-89 total score could be explained by the change in SF, seizure severity (Chalfont Seizure Severity Scale, CSSS), mood (Profile of Moods States, POMS), or adverse events (Adverse Event Profile, AEP). Associations among the variables were assessed using bivariate tests and multiple regression. Fifty-three participants completed enrollment and follow-up testing, seven at study termination. Mean QOLIE-89 total score improved from enrollment (49.4 ± 19) to follow-up (57 ± 21.3; $p = .004$). We also saw improvements in SF, POMS, AEP, and CSSS (all $p \leq .01$). Multivariable regression results showed QOLIE-89 at follow-up associated with improvements in POMS at follow-up ($p = .020$), but not with AEP, CSSS, or SF ($p \geq .135$). Improvement in QOL after treatment with CBD is associated with better mood but not with changes in SF, seizure severity, or AEP. Cannabidiol may have beneficial effects on QOL and mood that are independent of treatment response.

1. Introduction

As scientific methods have advanced and knowledge is accumulated through clinical research, the importance of measuring health-related quality of life (QOL) has been increasingly recognized as an important outcome measure for patients with chronic diseases in both the clinical and research settings [1]. Health-related QOL has implications on burden of disease and social impact due to disability on a global level [2]. It is well established that poorly controlled epilepsy is associated with low health-related QOL and that it has detrimental effects on mental health, physical functioning, social activity, and general health perception [3–6]. Quality of life in people with epilepsy (PWE) worsens with increased seizure frequency (SF) and severity, poor emotional well-being, depression, and longer duration of disease [4–10]. In particular, mood (anxiety/depression), longer duration of seizures, and adverse events are some of the strongest predictors of poor rating of QOL [11]. Further, in patients with treatment-resistant epilepsies (TREs), the correlation between QOL and drug-related adverse effects is higher than the correlation between QOL and SF [12,13], and in another study, depression was more likely predictive of QOL than SF [7]. Multiple

Abbreviations: QOL, quality of life; TRE, treatment-resistant epilepsy; ASD, antiseizure drug; CBD, cannabidiol; UAB, University of Alabama at Birmingham; VNS, vagus nerve stimulator.

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methods of assessing QOL in PWE have been developed in response to the increased awareness of QOL effects of poorly controlled seizures [14,15]. One such measure is the Quality of Life in Epilepsy-89 (QOLIE-89) instrument, which is a validated measure frequently used for QOL assessment in clinical trials of antiseizure drugs (ASDs) and taps multiple dimensions of QOL in PWE [14,16,17]. As the importance of QOL in epilepsy has been established, measuring QOL in clinical trials of potential ASDs has become an important outcome measure with similar emphasis as efficacy.

After years of only mostly anecdotal evidence, a highly purified oral solution of cannabidiol (CBD; Epidiolex®) has recently been shown to be an effective add-on ASD in Lennox–Gastaut and Dravet syndromes via phase III randomized, placebo-controlled trials [18–20]. Further, open-label expanded access programs in patients with TREs have also provided evidence toward CBD's efficacy [21–24]. In one open-label CBD study, children reported improvement in QOL after 12 weeks of treatment, which appeared to be distinct from its seizure-reducing effects [25]. A parent survey of children using CBD-enriched cannabis used for TRE demonstrated increased alertness, better mood, and improved sleep [26], and a study investigating the effects of a 50:1 ratio of CBD:tetrahydrocannabinol (THC) for seizures in children associated with Dravet Syndrome demonstrated statistically significant improvement in QOL after treatment [27]. To date, there are no published data on CBD's effects on QOL in adults with epilepsy, and the relationship between changes in SF and QOL in this population is also unclear. This study's objectives were to assess the QOLIE-89 scores in adult participants at the time of enrollment in a prospective open-label study of CBD for the treatment of epilepsy at the University of Alabama at Birmingham (UAB) and after approximately one year of treatment with CBD (or at study termination). In particular, we examined via exploratory analysis if observed changes in QOLIE-89 scores could be accounted for by change in mood (via enrollment and 1-year Profile of Mood States Total Mood Disturbance (POMS TMD)) [28], SF or severity [29] change while enrolled in the study, or change in Adverse Events Profile (AEP) [30] score. We hypothesized that QOLIE-89 scores would statistically and clinically improve after 1 year of CBD treatment, which, at least in part, would be independent of changes in mood, SF and severity, and AEP.

2. Material and methods

2.1. UAB CBD program

The State of Alabama-funded UAB CBD program has enrolled children and adults with treatment-refractory epilepsy for the use of a pharmaceutical formulation of highly purified CBD in oral solution (100 mg/mL; Epidiolex®; GW Research Ltd., Cambridge, United Kingdom) in an open-label safety study. The participants for this analysis were adults as QOLIE-89 was developed to assess QOL in adults with epilepsy [14,17]. For participation in this study, "treatment refractory" was defined as failing a total of ≥4 ASDs at adequate dose, including at least one trial of two concomitant ASDs. Many of the participants have seizures that also failed an epilepsy surgical procedure such as vagus nerve stimulator (VNS) placement or resective surgery. All potential participants had an application packet submitted by their primary neurologist; patients were permitted to self-refer provided that they were able to submit all necessary information for enrollment data. The packet was approved by a study approval committee with secondary approval by the study investigators at enrollment. Inclusion criteria included stable neurostimulator settings and ketogenic diet ratio for ≥3 months (if applicable), documentation of a detailed seizure diary 3 months prior to enrollment, and an Alabama residency. Exclusion criteria included history of substance abuse or addiction, use of cannabis or CBD-based product within the last 30 days, history of allergies to CBD or cannabis products or to sesame, felbamate therapy initiation within the last 12 months, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevation ≥5 times upper limit of normal, hemoglobin <10, hematocrit <30, or white blood cell count <2000, among others (all inclusion and exclusion criteria are available at www.uab.edu/cbd).

All participants were seen and evaluated in a dedicated research clinic that was held weekly. At the time of the enrollment visit, all participants and/or their legal representatives signed the consent form that was approved by the Institutional Review Board of UAB. The study was FDA-approved and registered with www.clinicaltrials.gov under the number NCT02700412 (adult arm). After signing an informed consent, participants were started on CBD at a dose of 5 mg/kg/day with dose increasing every 2 weeks by increments of 5 mg/kg/day to seizure control or tolerability at in-person visits to a maximum dose of 50 mg/kg/day. Participants and caregivers kept detailed seizure calendars, which, in combination with the reports of any side effects, led to the decision of CBD dose change. While ASD doses were required to be stable for at least one month prior to enrollment, after enrollment, physicians could change the standard ASD if the patients were reporting adverse events or if substantial improvements were noted in SF and severity with the addition of CBD. Data from some of the patients were previously reported [24].

2.2. Measures

On enrollment and at the 1-year visit, adult participants alone or with the help of a caregiver completed a battery of questionnaires, including the QOLIE-89 and POMS. At every study visit (including the enrollment and 1-year visits), the AEP was also completed. The Chalfont Seizure Severity Scale (CSSS) was obtained by physicians via interview.

2.2.1. QOLIE-89

The Quality of Life in Epilepsy inventory is a validated, 89-item inventory targeting health-related QOL issues specific to PWE [14,17]. The QOLIE-89 generates a total score (with higher scores indicating better QOL) based on 17 subscale scores that aim at evaluating 4 underlying dimensions of QOL in PWE: epilepsy-specific issues, cognitive status, and mental and physical health. Approximately a 10-point change on QOLIE-89 is considered clinically significant [31].

2.2.2. POMS

The POMS is a 65-item validated questionnaire that has been widely used to assess mood and has been used as a mood measure in epilepsy clinical trials [28]. The POMS consists of 6 subscales: tension or anxiety, depression or dejection, anger or hostility, vigor or activity, fatigue or inertia, and confusion or bewilderment. A total mood disturbance (TMD) score is derived from summing all subscales, and it reflects global assessment of mood rather than a particular state/subscale. Higher TMD scores indicate greater mood disturbance [28,32]. The depression/dejection subscale of POMS correlates well with Beck Depression Inventory (BDI) [33].

2.2.3. AEP

The AEP is a 19-item, validated questionnaire that assesses adverse events related to seizure medications [30]. Higher scores indicate a higher burden of adverse events. It is commonly used in the clinical trials setting to assess adverse events burden.

2.2.4. Seizure frequency and severity

Participants or caregivers were required to provide a seizure calendar for 3 months prior to enrollment. At every study visit, participants were required to bring an updated seizure calendar. Depending on the timing of the CBD titration, duration between study visits varied from 2 to 12 weeks. Therefore, for analysis, total seizure counts were summed between visits and averaged per 2-week periods. Seizure count was non-normally distributed (see Appendix Tables 1–2). Thus, it was coded as follows: <14/2 weeks, 14–50/2 weeks, and >50/2 weeks. This tripartite coding was designed to approximately equally distribute

participants and also to separate participants with less than daily seizures from those with daily or multiple daily seizures. One missing value for seizure count at 1 year was coded as the modal category of <14 based on the count from the previous period. This was done to preserve the sample size and did not affect the overall study findings (we also ran the analysis excluding this case). With the limitation of seizure diaries in this population [34], they were reviewed by the investigator with patient/caregivers for accuracy in reporting.

Seizure severity was measured by the CSSS, which is a reliable measure that assesses most disruptive aspects of seizures to patients, including seizure duration, time to return to baseline, and injury [29]. Higher scores indicate worse seizure severity. The CSSS was performed at enrollment and every follow-up study visit. Total CSSS summed across all seizure types at enrollment visit and at 1-year visit/early termination visit was used for this analysis. Of importance is that, similar to QOLIE-89, 10-point improvement in CSSS is considered to be clinically significant [29]. One outlier on CSSS at enrollment (value of 315) and one outlier on CSSS at 1 year (value of 219) were recoded to the second highest values (176 and 99 for enrollment and 1 year, respectively); no logarithmic transformations were appropriate based on these variables' distributions (see Appendix Figs. 1–2) [35].

The sample descriptive measures included sex, age (25 years and younger, 26–35 years, 36–45 years, and >46 years; see Appendix Table 3 for continuous distribution), age at onset (<18 years vs. 18 + years; see Appendix Table 4 for continuous distribution), did patient leave the study (yes/no), brain surgery prior to enrollment (yes/no), VNS prior to enrollment (yes/no), and number of ASDs tried prior to enrollment (10 or fewer vs. >10).

2.3. Analysis

Using the Mann–Whitney *U* test, we examined if the distributions of the QOLIE-89 total score at enrollment and at 1 year were similar among patients who left the study early and patients who remained in the study. Then, mean total QOLIE-89, POMS TMD, AEP, and CSSS scores at enrollment and 1 year (or early termination visit) were compared via paired t-tests while SF change was analyzed by using Wilcoxon signed rank test. Next, we assessed bivariate associations among pairs of continuous variables and pairs of continuous and binary variables by using Pearson correlations. This step was conducted to identify significant correlations and candidate variables to include in multiple regression (results are not included but are available upon request). Finally, we conducted a multiple regression analysis to determine if changes in QOLIE-89 scores could be accounted for by changes in POMS TMD, AEP, CSSS, or seizure count. In the regression model, QOLIE-89 total score at 1 year was the dependent variable. The independent variables included QOLIE-89 total score at enrollment, enrollment and follow-up POMS TMD, AEP, and CSSS scores, and enrollment and follow-up seizure counts. Results were considered statistically significant at $\alpha = 0.05$.

3. Results

Eighty adult participants were enrolled in the study. However, 27 did not receive QOLIE-89 because of the inability to complete the measure (e.g., because of severe cognitive handicap). Fifty-three participants had completed enrollment and qualifying follow-up visits (either 1 year or early study termination visit) at the time of the analysis. Of the 53 participants, seven withdrew from the study early because of lack of efficacy. Table 1 shows the demographic and clinical characteristics of the sample.

There were associations between patient characteristics, and the other study variables including age <25 years was associated with lower QOLIE-89 scores at enrollment ($p = .048$) while higher age categories were associated with higher QOLIE-89 score ($p = .015$). Cannabidiol dose was higher for males than females ($p = .040$), and seizure onset at age of 18 + years was associated with higher AEP score at 1 year than onset at age <18 years ($p = .023$). Furthermore, the distributions of the QOLIE-89 total scores at enrollment and at one-year or exit follow-up were not significantly different between patients who left the study early and the rest of the sample ($p = .847$ and $p = .807$, respectively for the enrollment and follow-up scores).

Table 1
Characteristics of the CBD patient sample (n = 53).

	n	%
Sex		
Male	27	50.9
Female	26	49.1
Age[c]		
25 years or younger	28	52.8
26–35 years	13	24.5
36–45 years	6	11.3
>45 years	6	11.3
Age of onset		
<18 years	45	84.9
18 + years	8	15.1
Type of seizures at enrollment[a]		
Generalized	18	34
Tonic–clonic	11	20.8
Absence	8	15.1
Myoclonic	5	9.4
Clonic	1	1.9
Tonic	5	9.4
Atonic	5	9.4
Epileptic spasm	2	3.8
Focal seizures	40	75.4
With impairment of consciousness	36	67.9
Without impairment of consciousness	12	22.6
Evolution to tonic–clonic	27	50.9
Epilepsy syndromes		
Focal	35	66
Lennox–Gastaut Syndrome	9	17
Symptomatic generalized epilepsy	4	7.5
Idiopathic generalized epilepsy	2	3.8
Dravet Syndrome	1	1.9
Tuberous sclerosis complex	1	1.9
Electrical status epilepticus during sleep (ESES)	1	1.9
Did patient leave study?		
No	46	86.8
Yes	7	13.2
Brain surgery (not inc VNS) prior to enrollment?		
No	36	68
Yes[b]	17	32
Corpus callosotomy	8	15.1
Temporal resection	3	5.7
Extratemporal resection	6	11.3
Implantation of intracranial electrodes (no resection)	5	9.4
VNS implanted prior to enrollment?		
No	34	64
Yes	19	36
Seizure count at enrollment[c]		
<14	22	41.5
14–50	16	30.2
>50	15	28.3
#AEDs tried prior to enrollment		
10 or fewer	35	66.0
10+	18	34.0

	Mean	Median	SD	Min	Max
Duration of epilepsy (years)	21.6	21.0	9.2	2.0	42.0
#Current AEDs at enrollment	3.2	3.0	0.8	1.0	5.0
CBD dose at 1-year visit (mg/kg)	27.8	30.0	17.3	0.0	50.0

Note: Several measures were categorized because of non-normal distributions.
[a] Note: 5 patients were coded as having both generalized and focal seizures.
[b] Note: 5 patients had a history of more than one surgical procedure.
[c] See Appendix for continuous distributions.

Table 2
Difference between seizure count distributions at enrollment and 1-year visit.

Seizure count	Enrollment	1-Year visit	p[a]
<14	41.5	62.3	
14–50	30.2	24.5	
>50	28.3	13.2	
			<.001

[a] Wilcoxon signed ranks test, two-tailed.

Statistically significant improvements were seen in total seizure counts between enrollment and at 1-year follow-up (Table 2) and in total QOLIE-89, POMS TMD, Chalfont total score, and AEP scores between enrollment and 1-year follow-up visits (Table 3). At enrollment, 28.3% of the study sample had >50 seizures every 2 weeks but only 13.2% had this SF at 1 year (Table 2). Over 30% of the sample had 14–50 seizures/2 weeks at enrollment, and 24.5% had this SF at follow-up. A total of 41.5% of the sample had <14 seizures/2 weeks at enrollment compared with 62.3% at follow-up. These changes were significant ($p < .001$). For seizure severity, the mean total CSSS score fell from 80.9 (SD = 40.1) at enrollment to 28.9 (SD = 25.8) at 1-year follow-up visit ($p < .001$) indicating statistical and clinical significance of these improvements (Table 3).

The mean QOLIE-89 score at enrollment was 49.4 (SD = 19) compared with 57 (SD = 21.3) at 1 year or study termination ($p = .004$; Table 3). These improvements were, on average, close to 10 points indicating that the observed improvements were not only statistically but may also clinically significant given the previously established clinical significance for QOLIE-89 of approximately 10 points [31]. The mean POMS TMD and AEP scores, on the other hand, fell by 9.7 ($p = .01$) and 5.8 points ($p = .001$), respectively, between enrollment and 1-year visit indicating improvements in both measures. The QOLIE-89 subscale scores were not normally distributed and, thus, total scores only were used in the analyses.

The regression results (Table 4) confirmed the increase in the QOLIE-89 score between enrollment and 1-year visit, which remained significant after adjusting for the enrollment and follow-up POMS TMD, AEP, CSSS, and seizure counts ($b = 0.608$, standard error (SE) = 0.152, $p < .001$). Profile of Mood States Total Mood Disturbance at follow-up was the only other variable in the model that had an independent and negative association with QOLIE-89 at follow-up ($b = -0.325$, SE = 0.134, $p = .020$), indicating mood problems being associated with lower QOL, after accounting for other factors. The multivariable model explained approximately 43% of the variation in the QOLIE-89 follow-up score (adjusted $R^2 = 0.425$).

Table 3
Average QOLIE-89, POMS, and Chalfont total scores at enrollment and 1-year visit.

	Mean	Median	SD	Min	Max	p[a]
QOLIE-89 total at enrollment	49.4	50.0	19.0	5.0	77.2	
QOLIE-89 total at 1-year visit	57.0	64.0	21.3	4.0	89.0	
Difference	−7.5		18.1			**.004**
POMS total at enrollment	34.7	31.0	33.5	−9.0	140.0	
POMS total at 1-year visit	25.0	21.0	33.3	−20.0	136.0	
Difference	9.7		26.6			**.010**
Chalfont total at enrollment	80.9	76.0	40.1	16.0	174.0	
Chalfont total at 1-year visit	28.9	22.0	25.8	0.0	99.0	
Difference	52.0		41.8			**<.001**
AEP total at enrollment	42.2	42.0	9.5	19.0	65.0	
AEP total at 1-year visit	36.4	35.0	11.6	19.0	61.0	
Difference	**5.8**		10.0			**<.001**

[a] Paired samples t-test, two-tailed. Significance of p less than or equal to (symbol) 0.05.

Table 4
Multivariable regression results.

	b	SE	Sig.
QOLIE 89 total score at enrollment	0.608	0.152	**0.000**
POMS total score at enrollment	0.057	0.115	0.624
POMS total at 1 year	−0.325	0.134	**0.020**
Chalfont score at enrollment	0.043	0.071	0.546
Chalfont score at 1 year	−0.164	0.106	0.132
AEP total at enrollment	0.102	0.346	0.771
AEP total at 1 year	0.318	0.327	0.337
Seizure count <14 at enrollment	6.637	6.969	0.346
Seizure count 14–50 at enrollment	−1.744	6.557	0.792
Seizure count <14 at 1 year	−4.209	8.593	0.627
Seizure count 14–50 at 1 year	−5.382	8.594	0.535
(Constant)	20.127	17.756	0.264
Adj. R-square = 0.418; df = 11.			

Note: Dependent variable was QOLIE-89 total score at 1 year. Reference group for seizure count at enrollment and 1 year was ">50". Significance of p less than or equal to (symbol) 0.05.

4. Discussion

This study confirmed our primary hypothesis that treatment with CBD is associated with statistically and clinically important increases in QOL among adult patients with TRE enrolled in a CBD-expanded access program, and that these improvements are at least partially independent of the improvements observed in other measures. Our study also demonstrated significant improvements in SF and severity, mood, and adverse events for adult participants with refractory epilepsy after treatment with CBD in an open-label safety study. Cannabidiol treatment appears to improve these patient outcomes. However, these changes appear to be largely independent of each other. One exception is that QOL at follow-up appears to depend on mood status at follow-up. Thus, improvements in QOL related to CBD treatment may be impeded by persistence of significant mood problems. Additionally, other research indicates that mood is a very strong predictor of QOL in people with refractory epilepsy [7,9,10]. The improvement in perception of overall wellbeing as demonstrated in the measures used in our study suggests that CBD may have effects on mood and QOL that are independent of seizure control. In a similar open-label CBD study in children, CBD was found to have positive effects on QOL that appeared to be at least somewhat independent of seizure control [25]. This has also been suggested with reported improvements in behavior by parents of children treated with artisanal forms of CBD [26]. These improvements may be, at least partially, explained by the positive effects of CBD on emotional processing that have been observed in functional imaging studies [36].

While our results of improved mood and QOL are promising, they may also have implications on a wider scale. The Epilepsy Impact Project was a mail survey of PWE in communities throughout the United States and asked questions about mood/depression, SF and severity, QOL, and doctor/emergency department visits [37,38]. People with epilepsy who completed the survey reported poorer QOL if they also reported symptoms of depression. Further, PWE with symptoms of depression perceived their seizures to be more severe and had a significantly increased number of doctor/emergency department visits compared with PWE without depression. Therefore, improvements in mood seen in our study could also have implications on health resource utilization, though this was not investigated specifically here.

One unexpected finding was that there was not a significant association between the changes in QOLIE-89 and AEP scores, despite both of these scores having significant improvements at follow-up. Previous research has shown that there have been strong linkages shown between adverse events and QOL — a relationship with a higher correlation than SF [12,13]. Thus, our finding suggests that there are positive effects of CBD on QOL that are independent of adverse effects. While the lack of

collinearity between QOL and AEP improvements in our study is unexpected based on previous result, it can be, at least in part, explained by the differences between our sample and patient with epilepsy samples included in other studies (e.g., higher levels of treatment-resistance or inclusion of patients with the most severe epilepsy syndromes).

There are several limitations to our study. First, the open-label nature of our study did not allow us to control for a placebo or expectation of efficacy effect [39] on SF and severity, QOL, mood, and adverse events. Such effects are frequently observed in studies of patients with neurological conditions, but they rarely are sustained for 1 year. The majority of our presented follow-up data are after one year of treatment, which should reduce or eliminate the expectation of efficacy effect if present here. Another limitation of this study is that we did not formally collect data on which participants utilized caregiver assistance in completion of the study questionnaires; this could have contributed to the observed results. Additionally, a component of increased social interaction during study visits might have contributed to some of the improvements in mood and QOL. Of note, CBD has been shown to interact with clobazam, with levels of its active metabolite increasing in the presence of CBD [40,41]. This could provide an additional benzodiazepine antianxiety effect and confound some of the improvements in POMS scores. However, testing this was beyond the scope of our analysis. Finally, CBD dose was not controlled in our analysis and varied widely in participants at the follow-up visit(s). Thus, it is unclear if the improvements seen were CBD-dose related.

Our results indicate that a highly purified CBD oral solution has positive effects on QOL that are partially independent of seizure control after 1 year of treatment. While promising, these results should be confirmed under more controlled conditions (i.e., compared against placebo). Further, once study visits are complete, it would be useful to determine if the improvements in mood, QOL, and adverse events are sustained with continued CBD treatment outside the setting of frequent study visits.

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Declaration of interest

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Appendix A

Appendix Table 1
Total seizure counts at baseline.

Seizure count	n	%
1.83	1	1.9
3.00	3	5.7
3.20	2	3.8
3.57	1	1.9
4.00	5	9.4
4.50	1	1.9
4.80	1	1.9
5.00	1	1.9
6.00	1	1.9
7.00	1	1.9
8.75	1	1.9
9.00	1	1.9
12.00	1	1.9
13.00	2	3.8
14.00	2	3.8
15.00	2	3.8
16.00	1	1.9
19.00	1	1.9
19.36	1	1.9
20.00	1	1.9
21.00	1	1.9
22.00	1	1.9
23.00	1	1.9
28.00	2	3.8
29.00	1	1.9
30.00	1	1.9
37.00	1	1.9
52.00	1	1.9
53.00	1	1.9
58.50	1	1.9
70.00	1	1.9
71.00	1	1.9
73.50	1	1.9
84.00	1	1.9
88.00	1	1.9
94.00	1	1.9
95.00	1	1.9
96.00	1	1.9
106.00	1	1.9
124.00	1	1.9
137.00	1	1.9
950.00	1	1.9
Total	53	100.0

Appendix Table 2
Total seizure count at 1-year follow-up.

Seizure count	n	%
0.00	2	3.8
0.20	1	1.9
1.00	3	5.7
1.57	1	1.9
1.67	1	1.9
1.83	1	1.9
2.00	4	7.5
2.36	1	1.9

Appendix Table 2 (*continued*)

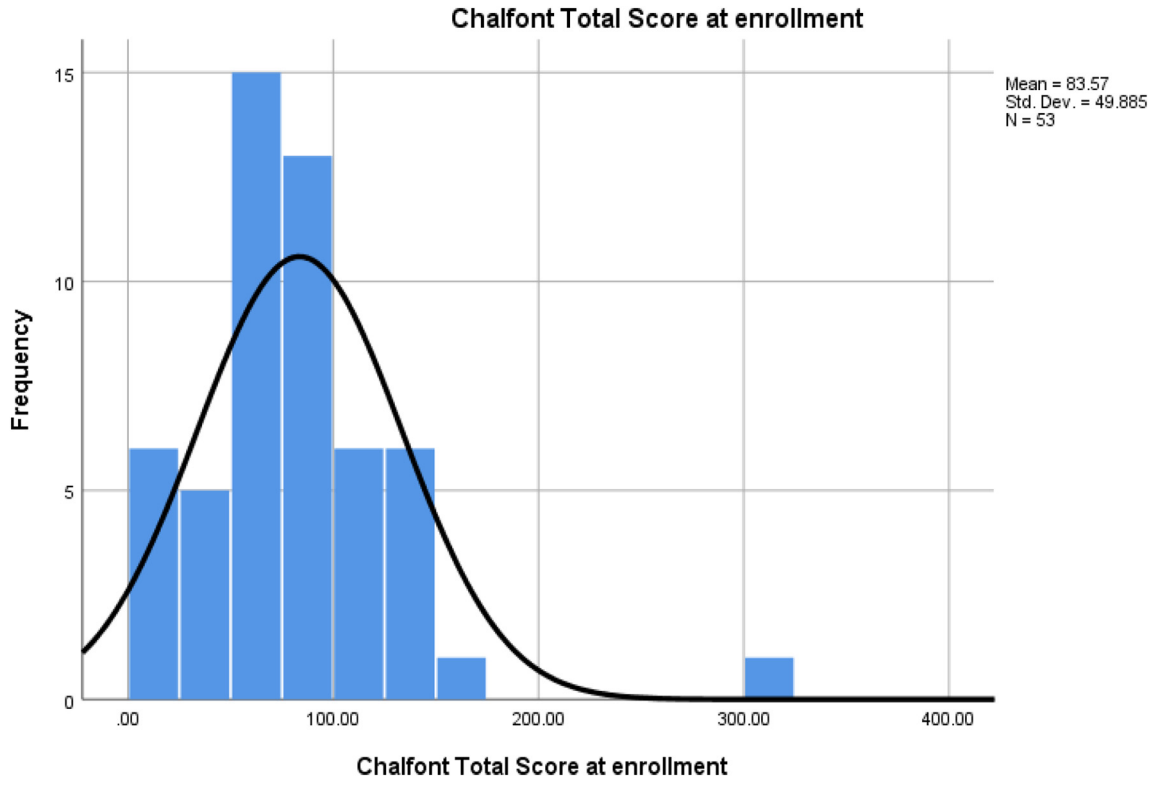
Seizure count	n	%
2.67	1	1.9
3.20	1	1.9
4.00	5	9.4
5.00	1	1.9
5.17	1	1.9
5.50	1	1.9
6.00	1	1.9
8.00	1	1.9
10.00	1	1.9
10.20	1	1.9
10.50	1	1.9
11.00	1	1.9
11.29	1	1.9
12.00	1	1.9
14.00	1	1.9
14.79	1	1.9
15.60	1	1.9
16.80	1	1.9
18.00	1	1.9
20.56	1	1.9
22.70	1	1.9
25.50	1	1.9
31.00	1	1.9
33.00	1	1.9
34.00	1	1.9
35.17	1	1.9
36.72	1	1.9
69.00	1	1.9
74.00	1	1.9
85.61	1	1.9
91.34	1	1.9
96.00	1	1.9
98.00	1	1.9
162.00	1	1.9
Total	52	98.1
Missing	1	1.9
Total	53	100.0

Appendix Table 3
Frequency and percentage distributions of age.

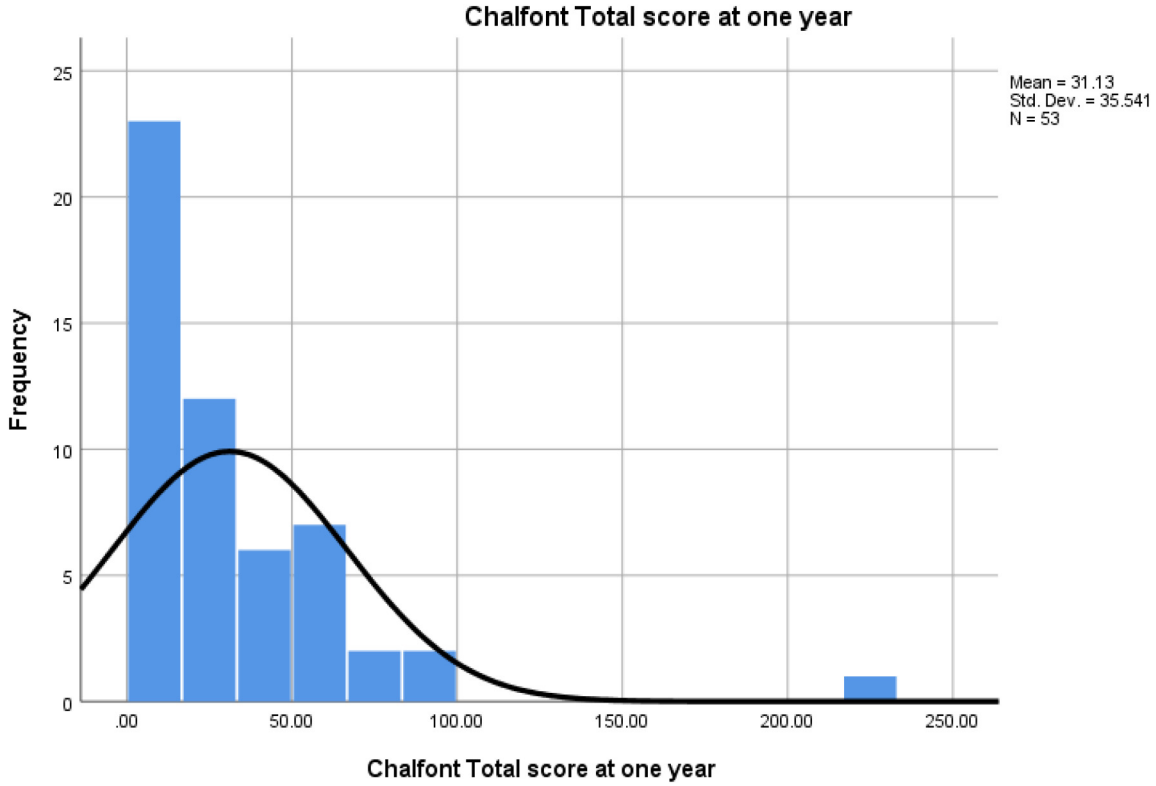
Age (years)	n	%
19	4	7.5
20	3	5.7
21	3	5.7
22	7	13.2
23	3	5.7
24	5	9.4
25	3	5.7
26	2	3.8
27	1	1.9
28	3	5.7
30	2	3.8
31	3	5.7
33	1	1.9
35	1	1.9
37	1	1.9
38	1	1.9
40	1	1.9
41	1	1.9
43	1	1.9
45	1	1.9
47	1	1.9
48	1	1.9
52	1	1.9
54	1	1.9
58	1	1.9
62	1	1.9
Total	53	100.0

Appendix Table 4
Frequency and percentage distributions of age of onset.

Age of onset (years)	n	%
0.00	5	9.4
0.25	1	1.9
0.50	3	5.7
1.00	6	11.3
1.10	1	1.9
2.00	4	7.5
3.00	2	3.8
4.00	3	5.7
5.00	4	7.5
6.00	1	1.9
7.00	3	5.7
8.00	4	7.5
9.00	1	1.9
10.00	1	1.9
11.00	1	1.9
13.00	1	1.9
14.00	3	5.7
16.00	1	1.9
18.00	1	1.9
22.00	1	1.9
23.00	1	1.9
24.00	1	1.9
27.00	1	1.9
29.00	1	1.9
32.00	2	3.8
Total	53	100.0



Appendix Fig. 1. Distribution of Chalfont total score at enrollment.



Appendix Fig. 2. Distribution of Chalfont total score at 1 year.

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