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Epileptic Disorders

ORIGINAL ARTICLE

Quality of life and cannabis use among patients with drug-resistant epilepsy—An observational study from a Canadian tertiary care referral center

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Abstract

Objective: Very few publications have reported the impact of artisanal cannabis use on overall quality of life among people with drug-resistant epilepsy. This study aimed to evaluate the association of artisanal cannabis use among adults with drug-resistant epilepsy with quality of life, and to determine if an association exists between Quality-of-Life in Epilepsy Inventory-31 (QOLIE-31) 'T scores' and different clinical variables.

Methods: This study included patients admitted to a Canadian tertiary care epilepsy center as part of a larger study. These patients were confirmed to have drug-resistant epilepsy by an epileptologist at the Ambulatory Epilepsy Clinic. Patients were categorized into cannabis users (CAN group) ($n = 25$) and Non-cannabis users (Non-CAN group) ($n = 21$). Data was collected on RedCap® for epilepsy and cannabis use details. These were analyzed for an association using a binary multivariable logistic regression model between QOLIE-31 'T scores' and age, sex, epilepsy duration, age at initiation of use, duration of cannabis use and psychiatric related comorbidity for all patients. Additionally, different 'T subscores' of the questionnaire were compared between the CAN group and Non-CAN group.

Results: A statistically significant difference between the CAN group and Non-CAN group for the T subscore 'energy and fatigue' ($p = .004$) was found, with the CAN group scoring higher. However, for the 'overall T score' between the two groups there was no statically significant difference ($p = .11$). Additionally, a significant negative correlation between 'overall T score' and cannabis use disorder ($p = .032$) was found.

Abbreviations: CUDIT-R, Cannabis Use Disorder Identification Test -Revised; HADS, hospital anxiety and depression scale; HRQoL, health-related quality of life; M.I.N.I, Mini-International Neuropsychiatric Interview; MSHQ, Marijuana Smoking History Questionnaire; QoL, quality of life; QOLCE, quality of life in childhood epilepsy; QOLIE-10, 10-ite, version of Quality-of-Life in Epilepsy Inventory; QOLIE-31, 31-item version of Quality-of-Life in Epilepsy Inventory; QOLIE-89, Quality-of-Life in Epilepsy Inventory; WHOQOL, World Health Organization Quality of Life.

Significance: This study provides new data on association of quality of life in epilepsy with cannabis use and can serve as a foundation for larger future studies to better assess this association.

KEYWORDS
cannabis, epilepsy, quality of life

1 | INTRODUCTION

In recent years, cannabinoids have been found to be an effective treatment for specific rare pediatric epilepsy syndromes like Dravet and Lennox–Gastaut syndrome.[1,2] On the other hand, legalization of cannabis in countries like Canada has been associated with widespread cannabis use for recreational purposes and medical indications.[3]

Epilepsy is a neurological disorder characterized by recurrent seizures affecting people of all ages, social classes, race and geographic location.[4] Moreover, medications currently available for epilepsy are effective in only two-thirds of patients.[4] These developments have significantly increased the interest of adults living with epilepsy in the potential benefits of cannabis and many have become cannabis users. A study by Kerr et al.,[5] reported a majority of patients in a tertiary care center used cannabis to improve their seizure control, but lacked a clear understanding of the potential risks or benefits of cannabis use for epilepsy.

There are few recent publications that have studied the overall impact of cannabis use on health among people with epilepsy (PWE).[6,7] However, there seems to be potential for cannabis to treat epilepsy.[8] For example, a study on 280 PWE using artisanal cannabinoid reported multiple health benefits.[9] Additionally, a recent 'umbrella' review study of randomized controlled trials and observational studies, found cannabidiol reduced seizure frequency, but increased events of pneumonia, gastrointestinal adverse effects and somnolence.[8]

Quality of life (QoL) in people with epilepsy worsens with increased seizure frequency and severity, poor emotional well-being and longer duration of disease.[10] However, there are often multiple seizure-related as well as non-seizure-related factors that potentially determine QoL. Tombini et al.,[11] found that QoL in adult PWE is predominantly affected by psychosocial, rather than epilepsy-related, factors.

Evidence for a relationship between cannabis use and QoL in people with drug-resistant epilepsy (DRE) is limited. A systematic review and a meta-analysis conducted by Goldenberg et al.,[12] found the relationship between health-related quality of life (HRQoL) and cannabinoid use for medical conditions to be inconclusive. Recently, however, some therapeutic intervention studies with cannabinoids have reported positive effects on QoL among PWE.[10,13] Despite this, there still remains an evidence gap about the impact of ongoing cannabis use on QoL among PWE.

Key points

- Cannabis use has no significant impact on overall QoL in drug-resistant epilepsy.
- Inhalational route for cannabis use is most common in this epilepsy population.
- Cannabis use disorder is significantly associated with poorer QoL in individuals with drug-resistant epilepsy.

This study was conducted to evaluate the association of artisanal cannabis use with QoL among adults in a tertiary care referral center with DRE.

2 | MATERIALS AND METHODS

This cross-sectional study was conducted as part of a larger study evaluating sleep and mood in adult patients living with epilepsy, conducted over a 3-year study period between 2019 and 2022. Epilepsy diagnosis and categorization as 'drug resistant' was confirmed by one of the epileptologists at the Ambulatory Epilepsy Clinic, hence referred for admission to the Epilepsy Monitoring Unit (EMU). 'Drug-resistant epilepsy' was determined when patients continued to report at least one seizure/1–2 months, despite trial with adequate doses of at least two appropriate anti-seizure medications.[14]

2.1 | Study population

Consecutive consenting PWE admitted to the EMU of our Canadian tertiary care epilepsy center during the study period were included. Patients with DRE were admitted to the EMU for presurgical evaluation, current seizure burden determination and/or characterization of additional types of spells suspected to be non-epileptic and/

or medication optimization in case of poor tolerability of medications with/without cognitive/other comorbidities affecting daily life.

Inclusion criteria: PWE from the study population who reported being active cannabis users, for recreational and/or medical indications (e.g. for sleep, pain or other conditions), were included (CAN group). Additionally, a control group was enrolled from the same population (consenting epilepsy patients admitted to the EMU), who were not cannabis users (Non-CAN group).

Exclusion criteria: Patients with previous diagnosis of a severe pre-existing neurological, psychiatric or medical disorder (limiting patients' ability to participate in study), including those with a diagnosis of polysubstance use disorders were excluded.

2.2 | Data collection

Data were collected on RedCap® for epilepsy characteristics, neurobehavioral comorbidities and pattern of cannabis use. These were analyzed for age, sex, duration of epilepsy, age at initiation of use, duration of cannabis use and psychiatric comorbidity and QoL for all patients.

Details regarding prior diagnosis of sleep-related or psychiatric comorbidity in this subset of patients were collected from hospital charts of included patients.

2.3 | Questionnaires used

Information on cannabis use was collected using the Marijuana Smoking History Questionnaire (MSHQ) administered to the CAN group.[15] Additional details about cannabis use like duration of regular use (in years) were collected from hospital charts. Details of cannabis use such as mode of consumption and formulation as well as if cannabis use was recreational or medicinal was also collected through questionnaires and entered into the study database. Further, information about mode of consumption (smoking/vaping/eating) and specific formulations used (CBD/THC and other cannabinoids) was also attempted to be extracted and entered into the study database.

The Cannabis Use Disorder Identification Test - Revised (CUDIT-R), also administered only to the CAN group, was used to determine presence of a cannabis use disorder.[16] The questionnaire consisted of eight questions with answers ranging from a scale of 0–4 (five options).[16] Some participants had selected an answer of five. This was taken to mean four to match scale options and assumed they meant five as in the fifth option of the scale. Total scores of eight or more indicated hazardous cannabis use.[16] Scores of 12 or more indicated a possible cannabis use disorder.[16] All questionnaires were administered at the time of the patient admission to the EMU or within 4 weeks of their discharge (study period—2019 to 2022).

To measure QoL in patients with epilepsy, the Quality-of-Life in Epilepsy Inventory-31 questionnaire was used for both groups. This is a self-rated questionnaire comprising 31 items grouped into seven multi-item subscales. The subscales consist of seizure worry, emotional well-being, energy/fatigue, cognitive function, medication effects and social function.[17] The inventory also includes a single item assessing overall QoL. A total score from 0 to 100 is derived by weighting and summing each subscale score with a higher score indicating a higher QoL.[17] A final T score is calculated using Table 3 from the QOLIE-31 manual.[17] These T scores represent linear transformations of the overall QoL score that produce a mean of 50 and standard deviation of 10 for a reference cohort.[17] An 'overall QoL T' score of less than 40 is considered poor.[18]

2.4 | Statistical analysis

'Overall QOLIE-31 scores' were calculated for both groups (CAN and Non-CAN). The scores were calculated using the QOLIE-31 scoring form which categorizes the 31 different questions into 7 subscores and subscribes different weights to each response. These were then transformed to QOLIE-31 'T scores' using Table 3 from the manual.[17] Descriptive statistics were calculated using Microsoft Excel® software and reported for each 'QOLIE-31 T subscore'. Additionally, the 'T scores' of the CAN group and Non-CAN group were then compared.

A Shapiro–Wilk test was performed to determine if the data set followed a normal distribution (p-value <.05). Majority of the data was found to not be normally distributed with many variables not being normally distributed (p-value > .05) for both CAN and Non-CAN groups.

For the continuous data, a non-parametric, independent samples Mann–Whitney U test analysis was performed to see if there were statistically significant differences between the 'QOLIE-31 overall T score' and 'T subscores' for the CAN and Non-CAN groups.

Further, a binary multivariable logistic regression correlation analysis was performed to test for an association between 'overall QOLIE-31 T score' and different important clinical variables. The 'overall QOLIE-31 T score' was used as the dependent variable and was made binary by categorizing the scores as high QoL (a score of 40 or more) and low QoL (a score lower than 40).[18] The multiple independent variables consisted of 'age', 'sex', 'epilepsy duration' and 'psychiatric related comorbidity', for

the Non-CAN group. For the CAN group, in addition to the variables already listed, 'age at initiation of use', 'duration of cannabis use' and 'cannabis use disorder' were included (Table 1).

3 | RESULTS

3.1 | Cannabis use among patients with DRE

During the study period between 2019 and 2022, a total of 51 patients fulfilled inclusion criteria of diagnosis of drug-resistant epilepsy and consented to participate in the study. Following informed consent, complete analyzable data on the pre-structured questionnaires was provided by 25 PWE (11 females; median age 32 [25]) for the CAN group, and 21 PWE (16 females; median age 52 [20] years) for the Non-CAN group (Table 1). Five patients did not complete the questionnaires; hence they could not be included. The majority of the patients in the CAN group (76% ($n=25$)) reported daily cannabis use and could be categorized in the 'Cannabis use disorder' category (68%) (Table 2). All cannabis users in the CAN group, including those who were categorized with cannabis use disorder, completed the QOLIE-31 questionnaire. Consumption of cannabis was majorly through bong (48%) (Table 2). All patients in the CAN group reported using cannabis for recreational purposes. Patients stated they were not aware of what type of cannabis they are consuming. Few patients ($n=5$) reported cannabis helping with their anxiety and two patients reported cannabis helping with their seizures although exactly how was not reported.

3.2 | QoL among patients with DRE who used cannabis versus those who did not

'Overall QOLIE-31 T score' was found to be low in both groups, but worse in the Non-CAN group (37 ± 11) than the CAN group (43 ± 13); however, this difference was not found to be statistically significant ($p=.11$). Among QOLIE-31 T subscores, 'energy and fatigue' was found to be significantly better in the CAN group (Table 3).

Using a binary multivariable logistic regression analysis, 'cannabis use disorder' was the only variable found to have a significant negative correlation with good QoL (QOLIE-31 T scores >40). No significant correlation was found between QoL and age, sex, epilepsy duration, age at cannabis use initiation, duration of cannabis use and diagnosed psychiatric comorbidity (Table 4).

4 | DISCUSSION

This study evaluating cannabis use and QoL among patients with drug-resistant epilepsy admitted to the EMU of a Canadian tertiary care referral center, suggests that nearly 50% of this specific population regularly use cannabis for recreational purposes. Moreover, there was no significant difference in QoL observed between the CAN group and the Non-CAN group.

4.1 | QoL and cannabis use in epilepsy

Our study results are similar to those of Strickland et al.,[9] who in a cross-sectional and longitudinal study on PWE,

TABLE 1 Demographic and epilepsy-related clinical details of patients with 'drug-resistant epilepsy' who reported to be cannabis users (CAN group) and those who do not use cannabis (Non-CAN group).

Patient characteristics	CAN group ($n=25$)	Non-CAN group ($n=21$)	p-value
Age (Median) (IQR)	32 (25)	52 (20)	.001*
Sex M:F	14:11	5:16	
Epilepsy type			
Focal	($N=2$)	($N=2$)	
Generalized	($N=22$)	($N=19$)	
Unknown	($N=1$)	($N=0$)	
Epilepsy duration (Median) (IQR)	8.5 (12)	17.0 (26)	.18
Number of current anti-seizure medications (N (%)) (Median) (IQR)	2 (1)	2 (2)	.33
Psychiatric comorbidity (N (%)) (those with existing diagnosis of a psychiatric disorder)	13 (52%)	5 (24%)	
Sleep-related comorbidity (N (%)) (those with existing diagnosis of a sleep disorder, including those on treatment for insomnia)	8 (32%)	4 (19%)	

Abbreviations: IQR, interquartile range; SD, standard deviation.

*Statistically significant.

TABLE 2 Details of cannabis use among patients with DRE (CAN group ($N=25$)).

Cannabis use characteristics	Observations
Age at initiation of use (years) (Mean ± SD)	19 ± 10
Duration (years) (Mean ± SD)	17 ± 16
Frequency of use	
2–3 times / week (N (%))	6 (24% of cannabis users)
Daily (N (%))	18 (76% of cannabis users)
Tried quitting (N (%))	20 (80%)
Duration of quitting (months) (Mean ± SD)	10.16 ± 18.55
Cannabis use disorder (CUDIT-R questionnaire)	
Hazardous use (N (%))	5 (20%)
Cannabis use disorder (N (%))	17 (68%)
Infrequent use (N (%))	3 (12%)
Cannabis mode of consumption	
Joint (N (%))	7 (30%)
Bowl (N (%))	1 (4%)
Bong (N (%))	11 (48%)
One-hitter (N (%))	1 (4%)
Ingestion (N (%))	3 (13%)
Details unavailable	2 (8%)

Abbreviations: IQR, interquartile range; SD, standard deviation.

found that those using artisanal cannabis had a marginally higher QoL (measured using the World Health Organization Quality of Life scale (WHOQOL)) compared to non-users, while the difference in WHOQOL scores was not statistically significant.

In an interventional study on patients with drug-resistant frontal lobe epilepsy, quality of life measured by the QOLIE-31 scale was compared between groups using highly purified cannabidiol and a placebo. The study found that after 8 weeks, the cannabidiol treatment group had significantly higher QOLIE-31 scores compared to the placebo group. This finding was not found at the four-week follow-up mark.[13] This study was conducted in a more controlled manner and with highly purified cannabidiol products, compared to the artisanal cannabis use reported in our study, hence their observations are not necessarily applicable to the larger epilepsy population using cannabis for various indications—recreational or medical.

In our study, we found the CAN group to score significantly better on the 'energy and fatigue' T subscore. In a prospective, open-label study, Rosenberg et al.[19] reported a statistically significant increase in caregiver-reported quality of life in childhood epilepsy (QOLCE) scores as well as 'energy and fatigue' subscores after 12 weeks of treatment with cannabidiol in children and young adults with severe childhood onset epilepsy. However, the study

TABLE 3 Quality of life in epilepsy T scores – Observations from QOLIE-31 questionnaire responses in patients with DRE, who use cannabis (CAN group) and those who do not use cannabis (Non-CAN group).

Quality of life assessment category		CAN group T scores ($n=25$)	Non-CAN group T scores ($n=21$)	p-value
Seizure worry	Median (IQR)	50.00 (23.50)	42.00 (16.50)	.070
	Mean ± SD	49.16 ± 13.43	42.52 ± 10.30	
Overall quality of life	Median (IQR)	40.00 (9.50)	39.00 (11.00)	.938
	Mean ± SD	37.56 ± 6.52	36.90 ± 8.74	
Emotional well-being	Median (IQR)	46.00 (18.00)	40.00 (15.00)	.056
	Mean ± SD	46.52 ± 11.33	39.52 ± 9.51	
Energy and fatigue	Median (IQR)	45.00 (19.00)	36.00 (12.00)	.004*
	Mean ± SD	45.76 ± 12.34	35.90 ± 7.20	
Cognitive	Median (IQR)	40.00 (21.00)	45.00 (16.50)	.903
	Mean ± SD	44.16 ± 13.02	43.76 ± 9.95	
Medication effects	Median (IQR)	54.00 (14.50)	52.00 (27.00)	.535
	Mean ± SD	50.92 ± 10.53	48.95 ± 12.38	
Social function	Median (IQR)	46.00 (19.50)	38.00 (13.50)	.072
	Mean ± SD	45.52 ± 11.21	39.86 ± 9.31	
Quality of life - total score	Median (IQR)	42.00 (21.50)	38.00 (17.00)	.110
	Mean ± SD	42.72 ± 12.61	36.90 ± 10.51	

Abbreviations: IQR, interquartile range; SD, standard deviation.

*Statistically significant.

TABLE 4 Binary multivariable logistic regression analysis of different predictors for QOLIE-31 T scores in whole epilepsy cohort.

	Observation: QoL (poor QoL = QOLIE-31 T score < 40, good QoL = QOLIE-31 T score 40–100)		
Variable	**Coefficient**	**Standard error**	***p*-value**
Age	−.12	.17	.50
Sex	−1.30	1.21	.29
Epilepsy duration	.055	.079	.48
Age at initiation of use	−.024	.169	.89
Duration of cannabis use (years)	−.16	.173	.35
Cannabis use disorder	−4.01	1.87	.032*
Psychiatric comorbidity	−.279	1.11	.80

*Statistically significant.

population was different from ours, and again effects of a standardized formulation was studied unlike our study which used artisanal cannabis.

Our study results differ from other studies that found cannabis use to significantly improve QoL scores in those with drug-resistant epilepsy. In a study by Gaston et al.,[10] QoL measured using the QOLIE-89 significantly improved after 1 year of cannabidiol oil treatment. Additionally, a study by Kochen et al.[20] with 44 patients found QoL significantly improved after 6 months of treatment in all items of the QOLIE-10 scale in patients. The design of both these studies differs from ours again, as we did not use a before and after comparison approach and instead used Non-cannabis users as a control. Our sample size as well as study population are similar to these studies, however, as previously noted, we studied patients using artisanal cannabis instead of cannabidiol/medicinal cannabis as used by these investigators.

4.2 | Common determinants of QoL in epilepsy and cannabis use

In our study, we found 'cannabis use disorder' to be the only variable significantly associated with a poorer QoL (negative correlation with good QoL). While no previous studies report data on QoL among people with cannabis use disorder specifically, Havlik et al.[21] recently reported mental health-related QoL (MHRQOL) to be negatively associated with treatment use among patients with cannabis use disorder.

In a larger study on epilepsy patients in general, Wahby et al.,[22] found that a history of psychiatric disease was significantly associated with QoL measured by QOLIE-10, and cannabis use only accounted for 12% mediation of this relationship. Cannabis use was also found to not significantly mediate the effects that seizure frequency had on QoL.[22]

Among other studies on determinants of QoL in epilepsy, cannabis use has not been factored in. In a study by Silva et al.,[23] conducted on 40 patients with focal DRE, diagnosis of a mood disorder and female gender were reported to be significantly associated with a lower QOLIE-31 score. Sociodemographic and epilepsy-related variables such as seizure frequency or epilepsy duration were not associated with QoL scores.[23] Further, overall psychiatric comorbidity as measured by the Mini-International Neuropsychiatric Interview (M.I.N.I.) was also not associated with the lower QOLIE-31 scores.[23] Findings are largely similar to ours, even while our focus was on cannabis using patients with drug-resistant epilepsy, and as mood disorders were the commonest among psychiatric comorbidity observed in our patient population also.

On the other hand, in their study with a larger sample size of 486, Siebenbroadt et al.,[24] reported that epilepsy patients had reduced QOLIE-31 scores associated with worry about new seizures and psychiatric comorbidity as assessed by the HADS score (Hospital Anxiety and Depression Scale). Differences in study population ('all epilepsy' versus 'drug-resistant epilepsy'), sample sizes and diagnostic tools used, might account for the variable observations in our study compared to theirs.

4.3 | Strengths, limitations and future directions

This study adds valuable data on QoL related literature in drug-resistant PWE and its relationship (or lack thereof) with cannabis use, demonstrating presence of 'cannabis use disorder' to have a significant negative correlation with QoL in this population. Use of validated tools for assessment of cannabis use and QoL, as well as clear patient selection criteria are the strengths of this study.

This was an observational cohort study and thus was limited to self-reported information and we did not have

control over cannabidiol dose, type of artisanal cannabis, frequency of administration or route of administration. However, this presents more 'real life' data on the subject, helping address patients' questions regarding association of cannabis use in their lives.

We also had a limited sample size. However, the sample was representative of the narrow population we were studying (patients with drug-resistant PWE admitted to the epilepsy monitoring unit during the study period), resulting in good generalizability for similar populations.

This study provides a foundation for future larger prospective cohort studies to better assess drug-resistant PWE and possibly use additional tools for assessment of cannabis use.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Test yourself

1. Which of the following cannabinoids has been shown to be effective in treating specific rare pediatric epilepsy syndromes such as Dravet syndrome and Lennox–Gastaut syndrome?
   A. THC (Tetrahydrocannabinol)
   B. CBN (Cannabinol)
   C. CBC (Cannabichromene)
   D. CBD (Cannabidiol)
   E. THCV (Tetrahydrocannabivarin)
2. What is a common challenge faced by patients with drug-resistant epilepsy (DRE) when using traditional anti-epileptic medications?
   A. High cost of medications
   B. Difficulty in obtaining prescriptions
   C. Medication does not work for one third of the patient population
   D. Limited availability of medications in rural areas
   E. Side effects are minimal and well-tolerated
3. Which of the following is a common method for measuring the quality of life in patients with epilepsy?
   A. Epilepsy Seizure Frequency Scale (ESFS)
   B. Beck Depression Inventory (BDI)
   C. Quality of Life in Epilepsy Inventory (QOLIE-31)
   D. Generalized Anxiety Disorder Scale (GAD-7)
   E. Visual Analog Scale for Pain (VAS Pain)

Answers may be found in the Supporting information.