MEDICAL CANNABIS:

A NEEDS ANALYSIS FOR PEOPLE WITH EPILEPSY

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ABSTRACT

Background and purpose. Medical cannabis may be effective treatment for refractory epilepsy. It is timely to seek users' and potential users' opinions in regard to its place in the management of epilepsy.

Materials and methods. An online survey was administered to members of an epilepsy support organisation in Western Australia. Experience with cannabis for management of epilepsy was explored, along with desire to trial a particular pharmaceutical formulation(s).

Results. People with epilepsy (33/71) and carers (38/71) participated. Fifty-four participants indicated no experience with medical cannabis, although 35, mainly with inadequate response to prescription medicines, were willing to ask for a prescription. Concerns included difficulty accessing cannabis and high cost of this treatment. Tablets/capsules was the most acceptable dosage form for development.

Conclusion. These findings suggest wide interest in trialling medical cannabis in individual cases of refractory epilepsy, despite the developing body of literature and some concerns about cost and procurement.

Key Words: epilepsy, seizures, medical cannabis, medicinal cannabis, survey

INTRODUCTION

Epilepsy is a chronic neurological disorder that affects approximately 50 million people worldwide, with a further 2.4 million new cases diagnosed every year (1). Conventional drug therapy aims to reduce or completely cease the occurrence of seizures (2); however, 30% of people have drug-resistant, uncontrolled or intractable epilepsy (3).

Treatment of drug-resistant epilepsy typically involves polypharmacy, which carries the risk of increased side effects (4). An alternate therapy that may be effective is medical cannabis (5), which has been reported to reduce seizure frequency in people with childhood-onset epilepsy such as Dravet syndrome and Lennox-Gastaut syndrome (6-12). The safety and efficacy of medical cannabis in epilepsy has not been well established, until recent developments, due to lack of formal clinical trials (5, 13, 14). This lack of high-level evidence has not precluded individuals from using cannabis for the management of epilepsy (15-18). There is limited insight into the prevalence of cannabis use in epilepsy in Australia, although a national study representing 976 people with epilepsy in Australia reported 15% of adults had used or were active users of medical cannabis, and 13% of children had been administered cannabis products by parents to manage their epilepsy (18). These prevalence estimates were not supported by data regarding users' experiences with, or preferences for, particular dosage forms.

Surveys have also reported users' perceptions of the efficacy of medical cannabis. Surveys of users in the United States (US), Canada, Mexico and Australia consistently reported their perception of the efficacy of medical cannabis, particularly amongst parents with children living with severe epilepsy (16, 18-25).

The recent legislative changes (The Narcotics Drug Amended Act 2016, s. 1.2.1) and media attention towards its use as a possible treatment option for epilepsy, have set the scene for advancement in clinical trials (26-28). Cannabidiol (CBD), a component of the cannabis plant, may be an alternative treatment for management of epilepsy (29). Recent studies, including randomised controlled clinical trials and open-label interventional trials, have reported a reduction in frequency of seizures in a range of epilepsy conditions including drug-resistant epilepsy, Lennox-Gastaut syndrome, Dravet syndrome, drug-resistant epilepsy in tuberous sclerosis complex, Febrile Infection-Related Epilepsy and Sturge-Weber syndrome (30-39).

Given the recent legalisation of prescribing and provision of medical cannabis in Australia and advancements in clinical trials, it is timely to seek users' and potential users' attitudes and opinions in regard to its place in the management of epilepsy (26, 27). Australian states/jurisdictions are governed by different legislation, and hence, prescribing protocols and availability of medical cannabis vary nationally (40). A state-wide focus was applied to the present study, with a view to replicating the study in other states.

AIM OF THE STUDY

This study aimed to investigate the perceived needs for medical cannabis in the management of epilepsy of adults with epilepsy and carers of a person with epilepsy in Western Australia (WA).

The secondary objectives of the study were:

1. To investigate (anonymously) and describe current usage and experiences with self-administration of medical cannabis;

2. To investigate opinions and understanding of efficacy and safety of medical cannabis in epilepsy;

3. To describe preferences for pharmaceutical formulation(s) of a medical cannabis product.

METHOD

Study Design

Approval for this research was granted by the Human Research Ethics Committee (HREC) of Curtin University (approval number: HREC2017-0311). This study was conducted via an online survey through a link distributed by an epilepsy support organisation, described below. Inclusion criteria required respondents to be at least 18 years of age, live in WA, and have epilepsy or care for someone living with epilepsy.

The questionnaire (available on request) comprised four open- and 22 closed-ended questions. Most questions were adapted from published opinion studies of people using medical cannabis for epilepsy (18, 41). Initial questions confirmed the inclusion criteria for the survey. Forced responses were only used to address the inclusion criteria and ensure progression through relevant question pathways.

Participants were asked about their current management of epilepsy, which included questions about health professionals managing the condition, the type of epilepsy, medication history, duration of therapy and current control with medications. A five-point Likert-type

scale was used to investigate concerns regarding use of medical cannabis. Respondents were also requested to rank preferences from a list of six dosage forms informed by review of the literature (42).

Multi-stage review was used to refine the questionnaire before its dissemination via an online survey platform. Due to the exploratory nature of this survey and lack of a 'gold standard', refinements to the draft questionnaire focused on face and content validation. Response options, progression pathways, clarity of wording and relevance of questions were reviewed independently by three academic researchers, resulting in changes to some terminology and addition of questions relating to legal concerns with the use of medical cannabis. An independent experienced consumer advocate was recruited through a formal network to review the questionnaire from a lay perspective. This consumer advocate, a parent of a child with severe epilepsy, suggested further changes to terminology. Scientific review of the questionnaire was also commissioned by the Curtin University HREC. Following all revisions, the reading age of the questionnaire was confirmed as grade 11, using Microsoft Word® (43).

Data Collection

The survey was conducted electronically using the Qualtrics® platform in July-August 2017. The electronic data collection offered the benefits of enhanced anonymity, convenience and minimisation of errors associated with manual data entry over a mailed or manually-distributed questionnaire (44). For this study, anonymity of responses was a key consideration due to the sensitive nature of the topic, and the survey link required dissemination through a third party for separation of the researchers from the participants.

There is no national register of people with epilepsy, hence no denominator, and therefore the best method to contact the target population was via a network. The network/distributor was Epilepsy Association of WA, who, with endorsement of their Board, posted the link to their *Facebook* page and distributed flyers at support group meetings attended by people with epilepsy and carers of people with epilepsy. The survey link was set to be unlinked to the respondent's IP address and expired once used, which discouraged multiple responses from one participant. Responses were monitored daily following distribution of the link, and a reminder was posted on the *Facebook* page every three calendar days. The survey was closed 42 days after the first distribution, guided by diminishing responses.

Data Analysis

Data from Qualtrics® were exported to Microsoft Excel®. Data were prepared for analysis by screening for missing variables, distribution of response options, and coding of free-text responses using an inductive approach. Analysis was performed using Excel®, with standard descriptive statistics and cross-tabulations to address specific research questions. The open-ended questions containing free-text responses were coded and analysed for breadth of reported experiences and opinions. The quantitative data were descriptively analysed for emerging trends. For the pharmaceutical formulations, the most common first preferences of the listed pharmaceutical formulations were identified.

RESULTS

The survey generated 97 responses. Twenty-six did not meet the inclusion criteria (24 were

non-residents of WA; one was under 18 years of age; one did not have epilepsy or was not a

carer for someone with epilepsy) and were excluded from analysis.

There were approximately equal numbers of respondents answering as the person with

epilepsy (33/71) versus as a carer (38/71). Over half (37/69) of the respondents had been

managing their/this person's epilepsy for over two years, yet around half (36/68) reported

little or modest control of the condition (p >0.05) (Table 1).

Who is the person with epilepsy? (n=71)	Myself (n=33)	Age range: 18 to 35 years (average: 35 years)
	A friend or family member I am caring for (n=38)	Age range: 10 months to 71 years (average: 14 years)
Gender of person with epilepsy (n=71)	Male	45%
	Female	55%
Residential location of person with epilepsy (n=71)	Metropolitan	67%
	Rural	13%
Type of epilepsy (n=62)	Generalised epilepsy	52%
	Partial epilepsy	29%
	Other	19%
Duration of therapy (n=69)	Less than two years	46%
	More than two years	54%
Level of control (n=68)	Good control	47%
	Moderate control	32%
	Little or no control	21%

Table 1. Demographic and clinical profile of respondents

The majority of responses relating to the health professional(s) involved in management of

the person's epilepsy (respondents could select as many as applicable) indicated care by

specialists (64/157, 41%) and/or general practitioners (36/147, 24%). Pharmacists, nurses and other allied health professionals totalled 35% of responses (n=47).

Valproate, levetiracetam and carbamazepine were the most frequently identified prescribed medicines (126/299, 40%) for management of this person's epilepsy (Figure 1).
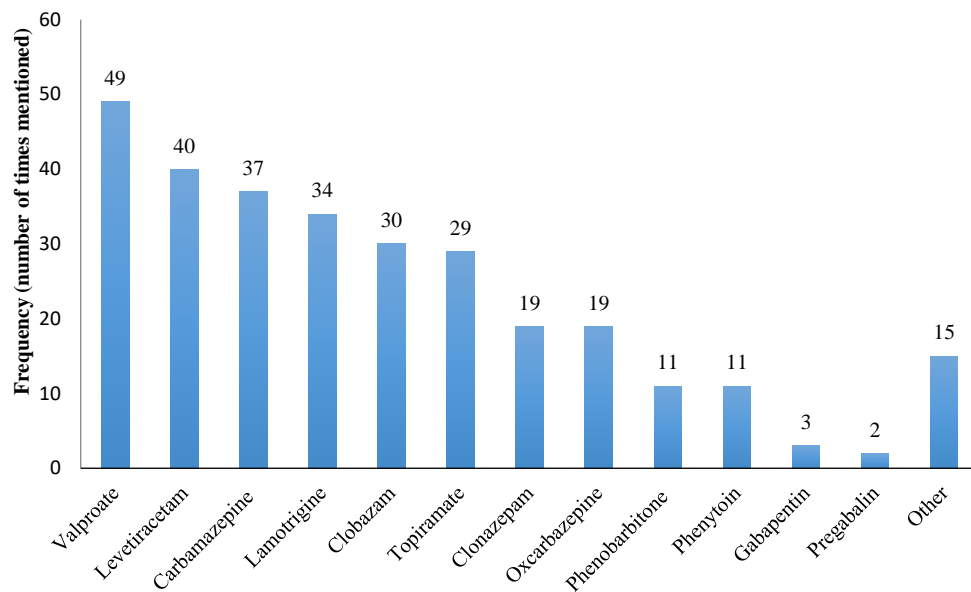

Figure 1. Prescription medications tried or currently used for the management of epilepsy (n=299*)
*Respondents could indicate as many as applicable
[colour print not required]

The majority of respondents (54/70, 77%) indicated using only prescription medications, while 19% (13/70) indicated using alternative treatment options that included herbal or natural medicine, a ketogenic diet, neurosurgery and avoidance of triggers. Three respondents (4%) indicated no current treatment. Of the respondents using alternative management, 12 respondents were also using prescription medications. Around half (46%, 25/54) were using more than one prescription medication, yet little or modest response was reportedly attained in the majority of respondents. Chi-square analysis found no significant association (p <0.01).

Use of medical cannabis

Sixteen of 70 respondents to the question about experience with cannabis for epilepsy indicated that medical cannabis was being used or had been used to manage their/the person's condition. Of these, nine respondents had stopped using/administering medical cannabis, with 17 reasons indicated, principally concerns about the illegal status of cannabis (n=5), stigma associated with its use (n=4) and limited supply (n=3). Methods of administration used by these respondents included oil or tincture taken orally, oral consumption (hash cookies), smoking and/or vaping. Eleven of the respondents reporting experience with medical cannabis indicated they had used it on most days of the week. Inadequate pharmaceutical control of the person's epilepsy was reported by 12 of the 16 respondents.

Fifty-four respondents indicated no experience with medical cannabis, yet 35 of these respondents indicated that they would be willing to ask a doctor to prescribe it. Five of the respondents were not favourable to requesting a prescription, while the decision by the remaining 15 respondents would be dependent on the safety and efficacy profile, ease of

access and cost of the medical cannabis product. Of 45 respondents willing to try medical cannabis, 29 indicated poor control with current medications and 17 indicated good control. One respondent reporting inadequate conventional management reported, *"I have heard a lot about medical cannabis, and as my epilepsy seems to be drug resistant, I have no choice but to try anything that will enable me to live a normal seizure-free life. The side effects of my current medications change my personality, so I would also be interested in something that has limited side effects."*

Perspectives about medical cannabis

Most respondents perceived that medical cannabis was safer than prescription medicines and efficacious for epilepsy (Figure 2). This was supported by a number of free-text responses, whereby 26 out of 53 respondents reported they would be willing to try medical cannabis. An exemplary quotation was, *"I believe it has a high chance of helping, and I believe that we should have the freedom and right to choose this as an option, as it is not harmful. Marijuana has never killed anyone, yet epilepsy drugs can make you depressed and suicidal. I've always wanted the option of a natural way to go versus the drugs, so having the choice to take medical marijuana would be a big deal for me."*
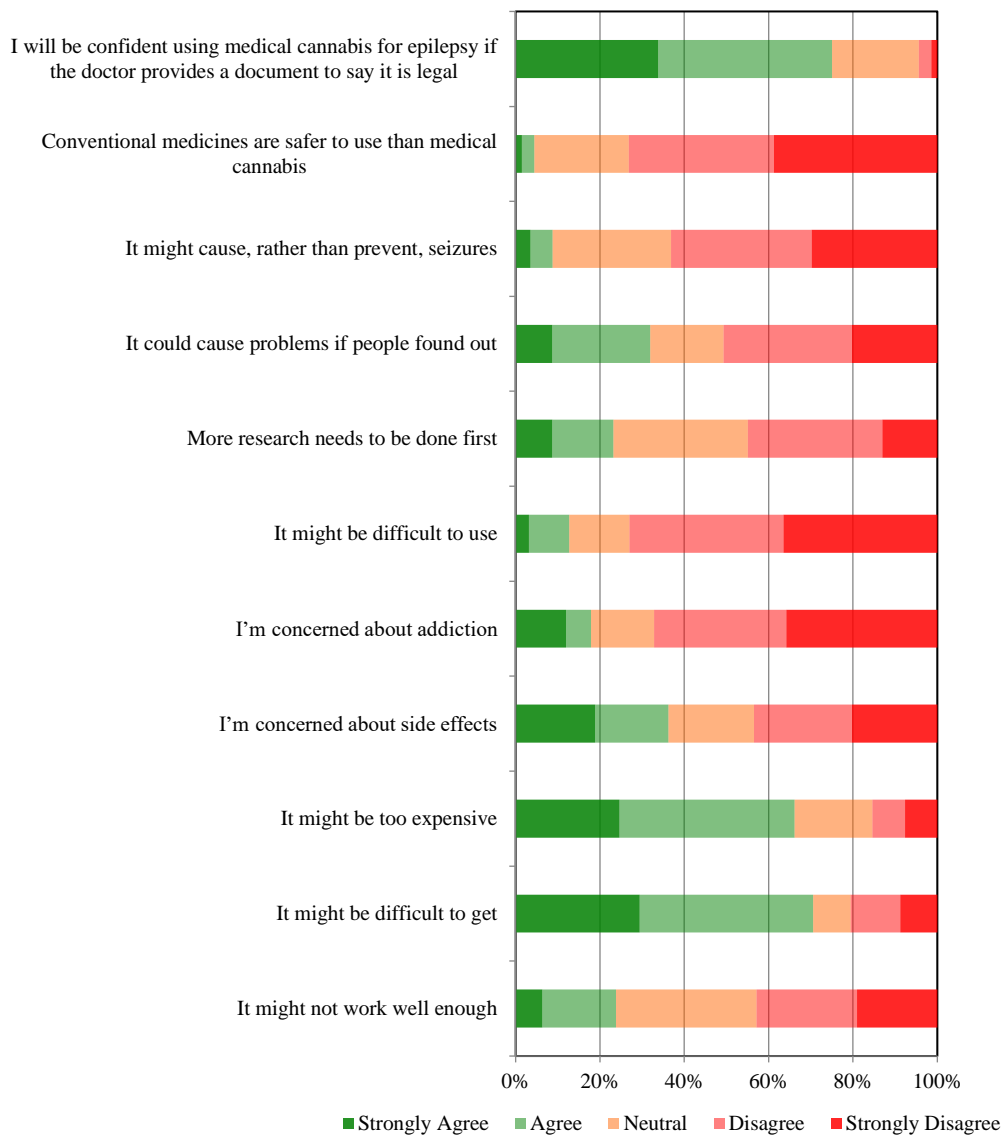
Figure 2: Concerns with use of medical cannabis (n=71 respondents)
[colour print required]

The availability and accessibility of medical cannabis was a concern highlighted by several

respondents. Respondents indicated that it was difficult to access medical cannabis due to

prescribing protocols; the cost of the medication was another potential issue. As stated by one

respondent, *"As far as I am aware, there is not a [doctor] able to prescribe in our area, I*

don't know if it will work, unsure if relevant to treat this type of epilepsy, from what I have

seen it would be unaffordable." Half of the respondents (n=37) indicated that they would be

willing to pay more than the Pharmaceutical Benefit Scheme[#] price for the medication, which was AU$6.30 for concessional patients and AU$38.80 for non-concessional patients, while 15% (n=11) said they would not, and one-third were unsure.

Formulation preferences

Overall, oral tablets or capsules were the most popular preference for administration of medical cannabis. Other listed options were sublingual drop or spray, oral liquid, inhaler, suppository and liquid for enteral feeding. Of the listed options, medical cannabis in the form of a suppository was the least popular dosage form, with one respondent quoting; "*I will not let them force us into suppositories.*" An oral liquid or a sublingual drop or spray were other options considered to be favourable by respondents, and these options were more popular amongst parents of children with epilepsy.

Some concerns in regard to the dosage form included palatability, colour and ease of administration. As stated by two respondents, "*Must think of taste, size, colour and ease of use for patients and carers*" and "*Whatever is safest for the person, and seeing as it is for epilepsy, a route that minimises choking.*" One respondent stated, "*Inhaling it makes it seem more stigmatised.*"

No difference was evident when taking into account experience with other forms of cannabis products.

[#] Australian Government medicines subsidy scheme

DISCUSSION

This study highlighted a perceived need for medical cannabis in the management of epilepsy. The majority of respondents favoured use of medical cannabis in epilepsy, despite limited evidence from clinical trials for its safety and efficacy. This can be attributed to the recent media attention around the area and legislative changes in Australia, in relation to manufacturing, prescribing and access of medical cannabis (26, 27, 40). This positivity has been confirmed by previous studies, where adults and parents of children with epilepsy reported a high level of efficacy or perceived sufficient evidence for use of medical cannabis in epilepsy (16, 18-25).

A sample size could not be predicted, as the survey was advertised through a third-party organisation's *Facebook* page, with no known number of eligible respondents; however, the number of responses was adequate to conduct descriptive analysis. Overall, the current study demonstrated more interest in the area than the inclusion criteria could accommodate.

There were almost equal numbers of people answering for themselves and on behalf of a person with epilepsy. Given the mix of respondents answering for themselves versus another person, it is evident that the survey provided a voice for those with high-care needs.

The sample comprised a balance of people with good control (47%) versus poor control (53%). Approximately 30% of people with epilepsy do not respond to conventional drug treatment; the current study therefore attracted a slight over-representation of people with refractory epilepsy (3). This suggests interest in medical cannabis amongst people with

refractory epilepsy, with those reporting poor control more open to medical cannabis to gain adequate control. Suraev et al. identified that 70% of parents of children with epilepsy and 45% of adults indicated treatment-resistant epilepsy as one of the major reasons for using cannabis products (18). Their level of control was not associated with the duration of therapy (p>0.05); further investigation is required to confirm this. The current results are also suggestive of the frustration and desire amongst people with epilepsy to try complementary and alternative medicine (CAM) options. This was indicated by respondents using alternate methods for the management of epilepsy, such as the ketogenic diet, natural/herbal medicines, neurosurgery and avoidance of triggers. Use of CAM has been studied in people with epilepsy, with marijuana the most commonly used (15). As suggested by the free-text responses in the current study, medical cannabis is perceived as a natural medication and is therefore associated with fewer and/or milder side effects, potentially contributing to its high acceptance.

Valproate, carbamazepine and levetiracetam were identified as the most commonly prescribed anti-epileptic medications. These are first-line agents for most forms of epilepsy (45). Of the respondents reporting use of prescription medications, more than half indicated they were using more than one medication, yet more than half reported little or no control of their epilepsy (p< 0.01). This suggests a degree of failure of conventional drug treatment in management of epilepsy in this sample, and explains their interest in alternative methods such as medical cannabis. The safety and efficacy profile of cannabinoids for use in epilepsy is under clinical trial (46). There is some evidence to suggest CBD interacts with some anti-epileptic drugs, such as valproate and clobazam (46, 47). Furthermore, CBD is metabolised by enzymes in the cytochrome P450 family, mainly by the CYP3A4 isozyme, and therefore medications that inhibit or induce this isozyme, such as carbamazepine, phenytoin and

phenobarbitone, could affect therapeutic outcomes (45). CBD is also a potent inhibitor of CYP2C19, CYP2D6 and CYP2C9 isozymes. This further increases the number of potential drug interactions for example with clobazam, topimarate and zonisamide (48). Therefore, people with epilepsy and health professionals willing to prescribe CBD need to be vigilant regarding drug interactions, and patients educated to avoid cessation or initiation of CBD therapy without consulting their health professionals.

The reported prevalence (22%) of experience with medical cannabis for control of epilepsy in the current study was comparable to the 28% reported by Suraev et al. The anonymity of both surveys and inclusion of adult patients and carers was intended to encourage reporting of experience with medical cannabis. Measurement of population prevalence of use was beyond the scope of this study, and until medical cannabis prescribing or dispensing records are centralised, remains unachievable.

In the current study, around half of the people who indicated experience with medical cannabis had discontinued its use. The small sample provides some insight into the associated reasons. Limited supply and stigma associated with use of medical cannabis could reduce as the industry develops in Australia, and use of medical cannabis becomes more widely prescribed and socially acceptable. Despite legalisation of prescribing of medical cannabis, there is anecdotal evidence of limited uptake of prescribing, due to stringent access protocols and the need for trial-and-error decision making by prescribers (40). This has also been reported by Mathern et al., whereby very few specialists supported use of medical cannabis in epilepsy, as there were limited safety and efficacy data to support its use (41). More data from clinical trials and more evidence-based prescribing decision tools may encourage greater interest and confidence amongst prescribers, leading to increased access to the

medication. Respondents to the current study indicated willingness to approach their prescribers to trial medical cannabis. Further research into these behaviours is warranted.

There is no published research on pharmaceutical dosage forms for medical cannabis for use in epilepsy. Lack of pharmaceutical formulations or products brings the challenge of standardisation and consistency, which can impact efficacy of the product. The survey by Mathern et al., involving epileptologists, neurologists, general practitioners, allied health professionals and patients, indicated 78% were in favour of a pharmaceutical-grade product (41). Tablets or capsules were the most popular choice, presumably due to familiarity with these dosage forms. However, a range of dosage forms should be considered to accommodate paediatric patients and patients with swallowing difficulty. Oral liquid and sublingual tablets were dosage forms that were ranked after oral tablets and capsules. Further studies are needed to investigate concerns with particular certain dosage forms in epilepsy; for example, oral formulations of cannabinoids present challenges with bioavailability, due to an extensive first-pass effect (46). The current study provides some insight for the preferences of dosage forms for people with experience with cannabis products. Additional research could investigate associations between dosage forms of cannabis already tried and preference for pharmaceutical dosage forms.

Despite the modest response, this study provided unique insight into the preferences for dosage forms of medical cannabis for epilepsy. The state of WA is isolated from the majority of the population in Australia, and therefore the findings support the current development of the local cannabis industry, which will likely be self-sustaining. A range of perspectives was obtained from patients and carers of people with epilepsy and spanning naïve and

experienced users of cannabis for management of epilepsy. The opinions were also equally received from people reporting good control and poor control of their/the person's epilepsy.

The potential for response bias is noted, as majority of the respondents were favourable towards use of medical cannabis in epilepsy. This is, however, suggestive of the interest in the topic, and people passionate about availability of non-traditional medications were more likely to participate in the survey. The study was exploratory, and given that the study did not aim to determine population prevalence, response bias was considered acceptable.

The comprehensive, inclusive and exploratory nature is a strength of the study. The survey could be replicated in other jurisdictions to further inform the development of suitable pharmaceutical dosage forms to suit a majority of people with epilepsy and administration by carers.

CONCLUSION

This study provides preliminary evidence that there is a wide interest and reported need for medical cannabis in epilepsy. Despite the developing body of literature to support its use in the management of epilepsy, there seemed to be a high acceptance and willingness to try medical cannabis as an option, regardless of the status or control of their condition. A high level of perceived efficacy and safety was noted amongst respondents, indicating the interest and need for an alternative treatment option for people with epilepsy. This study provides some insight into the opinions of people with experience with medical cannabis and highlights some concerns faced by these individuals. Further investigation in a larger sample

is warranted to assess the need of medical cannabis in epilepsy and preferences of a pharmaceutical-grade product.

This study also calls for training of health professionals on prescribing and dispensing of medical cannabis to meet the needs of people with epilepsy, and patient education in regard to access and use of medical cannabis to minimise harm and optimise health outcomes.

ACKNOWLEDGEMENTS

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