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# An Australian nationwide survey on medicinal cannabis use for epilepsy: History of antiepileptic drug treatment predicts medicinal cannabis use

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ABSTRACT

Epilepsy Action Australia conducted an Australian nationwide online survey seeking opinions on and experiences with the use of cannabis-based products for the treatment of epilepsy. The survey was promoted via the Epilepsy Action Australia's main website, on their Facebook page, and by word of mouth. The survey consisted of 39 questions assessing demographics, clinical factors, including diagnosis and seizure types, and experiences with and opinions towards cannabis use in epilepsy. A total of 976 responses met the inclusion criteria. Results show that 15% of adults with epilepsy and 13% of parents/guardians of children with epilepsy were currently using, or had previously used, cannabis products to treat epilepsy. Of those with a history of cannabis product use, 90% of adults and 71% of parents reported success in reducing seizure frequency after commencing cannabis products. The main reasons for medicinal cannabis use were to manage treatment-resistant epilepsy and to obtain a more favorable side-effect profile compared to standard antiepileptic drugs. The number of past antiepileptic drugs tried was a significant predictor of medicinal cannabis use in both adults and children with epilepsy. Fifty-six percent of adults with epilepsy and 62% of parents/guardians of children with epilepsy expressed willingness to participate in clinical trials of cannabinoids. This survey provides insight into the use of cannabis products for epilepsy, in particular some of the likely factors influencing use, as well as novel insights into the experiences of and attitudes towards medicinal cannabis in people with epilepsy in the Australian community.
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## 1. Introduction

Despite the availability of more than 20 prescription anti-epileptic drugs (AEDs), conventional treatment approaches prove ineffective in approximately 25–30% of people with epilepsy [1,2]. Treatment resistance has a well-defined trajectory: seizure freedom is typically achieved with the first two appropriate AEDs tried, with the probability of achieving "sustained" seizure-freedom declining significantly with each successive drug treatment [3,4].

Uncontrolled epilepsy is associated with an increased risk of morbidity including neuropsychological impairment, psychiatric and behavioural disturbances, and psychosocial difficulties [5–7]. Use of multiple AEDs, in an attempt to overcome treatment-resistance, can also cause impairment, with individuals taking two or more AEDs self-reporting greater cognitive, emotional, and behavioral side effects than those on a single drug regimen [8]. Failure of conventional treatments, coupled with intolerable side effects during polypharmacy, may lead patients to embrace untested treatment options, such as cannabis and its derivatives, to try to manage seizures.

The endogenous cannabinoid system (ECS) is a complex neuromodulatory system that consists of lipid-like signalling molecules (endocannabinoids) that interact with cannabinoid CB1 and CB2 receptors and other targets in the central and peripheral nervous system [9]. The ECS plays a major role in regulating neuronal excitability, neuroinflammation, and excitotoxicity within the brain [10,11]. Abnormalities in the ECS have been identified in people with various forms of epilepsy [12,13], and genetic and pharmacological modulation of the ECS in rodents causes major effects on seizure susceptibility [10]. Cannabinoids have also been shown to have actions at a range of epilepsy-relevant targets including GABA-A and TRPV receptors in preclinical models [10,14–16]. These observations have contributed to a growing realization that cannabinoid ligands could be novel therapeutic agents for epilepsy.

The use of plant-derived cannabinoids for seizure reduction has been described for centuries [17], while the last decade has witnessed

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an unprecedented media and community interest in cannabinoids in the management of epilepsy centered around high-profile case studies (e.g. Charlotte Figi) [18]. Past systematic reviews have concluded that there is insufficient evidence to support or refute the use of cannabinoids in treating people with epilepsy [19,20]. More recently, one open-label, one expanded access, and a small number of yet-to-be published placebo-controlled clinical trials have reported positive outcomes with cannabidiol (CBD), a major non-intoxicating cannabinoid found in some strains of the cannabis plant, in various forms of severe pediatric epilepsy [21,22]. However, CBD is not yet available as a registered medicine, and the use of artisanal cannabis-based oil and liquid extracts continues, with an increasing number of anecdotal reports of perceived success. This increasing use of untested cannabis-based products raises some concerns as, in addition to the uncontrolled nature in which some of these products are manufactured, the short- and long-term safety profile of cannabinoid use in humans, particularly in children and in combination with AEDs, is unclear and requires stronger scientific evaluation [2].

A number of recent surveys of cannabis extract use in treating childhood treatment-resistant epilepsy suggest a possible role for cannabis extracts in reducing seizure frequency [23–27]. A large cross-sectional survey of medicinal cannabis users in the United States indicated that the majority of people surveyed (61.2%) were using medicinal cannabis to treat chronic pain, with only 55 (3.8%) of the total cohort using medicinal cannabis for epilepsy or other seizure disorders [28]. However, compared to the other disorders, those using cannabis for epilepsy had among the highest proportion of self-reported perceived efficacy.

Recent regulatory changes and high profile scientific initiatives focused on medicinal cannabis in Australia have intensified community debate and the desire for information on this topic [29,30]. Accordingly, the current study aimed to survey frequency of cannabis extract use for epilepsy in the Australian community, reasons for and against use, and possible factors contributing to trying cannabis extracts to manage epilepsy. Our two targets for the survey were: (1) adults with epilepsy, and (2) parents/guardians of a person with epilepsy.

## 2. Methods

### 2.1. Survey

An on-line survey was developed, consisting of 39 questions that measured demographic factors, clinical factors (including diagnosis and seizure types), past treatment history for epilepsy, and attitudes and opinions of cannabis use in epilepsy. Study data were collected by online survey software, Survey Monkey®. The survey link was posted for ten days, and promoted through Epilepsy Action Australia (EAA), a national non-profit organization that provides education and services to people with epilepsy and their families, via their website and emailing list, the EAA Facebook page, and word of mouth.

The study population was any individual who has, or knows someone who has, epilepsy. All responses captured were anonymous and the automatic IP address capture feature on the software was deactivated to maintain confidentiality. The survey's preamble advised participants not to include any identifying information (e.g., names, locations) in questions allowing unlimited free script. Overall, there were 1275 respondents in the survey. Respondents' answers were excluded if they: 1) identified themselves as grandparents, siblings, or "other" of the person with epilepsy (n = 208), and 2) failed to respond to Question 15: "Have you or the person with epilepsy tried any form of medicinal cannabis for seizures?" (n = 91). The former was to limit the degree of separation between the respondent to the survey and the person with epilepsy. Question 15 referred to both past and present use of medicinal cannabis for treatment of epilepsy. This resulted in 976 eligible responses, consisting of respondents who identified themselves as "self with epilepsy" (45.5%, 444/976) or a "parent and/or guardian" of an individual with epilepsy (54.5%, 532/976).

**Table 1**
Demographic information of respondents to the Epilepsy Action Australia: cannabis use in epilepsy survey.

| | N (%) |
|---|---|
| Total respondents | 976 |
| Age of person with epilepsy | |
| Children | 389 (39.9) |
| 0–5 | 91 (9.3) |
| 6–12 | 192 (19.7) |
| 13–17 | 106 (10.9) |
| Adults | 587 (60.1) |
| 18–24 | 119 (12.2) |
| 25–64 | 448 (45.9) |
| 65 + | 20 (2.0) |
| Geographical location | |
| NSW | 376 (38.5) |
| QLD | 215 (22.0) |
| VIC | 148 (15.2) |
| WA | 133 (13.6) |
| SA | 44 (4.5) |
| TAS | 35 (3.6) |
| ACT | 15 (1.5) |
| NT | 10 (1.0) |

Perceived efficacy was assessed with a dichotomous question: "Do you consider medicinal cannabis successful in managing seizures for you or the person with epilepsy? Yes/No." Two-thirds of the survey questions were dichotomous or multiple-choice options, while the remaining permitted free-text responses (see Data S1). Pre-existing survey data-set was accessed, used, and published in non-identifiable form, and did not require ethics approval according to University of Sydney Human Research Ethics[1].

### 2.2. Data analysis

Responses were uploaded onto an electronic spreadsheet and tabulated. Data were analysed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA). Thirty-four variables, including demographics and medical history relating to the epilepsy, were tested as potential predictors for medicinal cannabis use. The dependent variable (whether the individual had used medicinal cannabis or not) was dichotomous, and the independent (predictor) variables were a mix of dichotomous and continuous variables. Each independent variable was first entered into a univariate binary logistic regression analysis. Variables that predicted medicinal cannabis use with a degree of significance of $p < 0.1$ were entered into a multivariate forward conditional binary logistic regression analysis [31,32]. Two multivariate analyses were conducted, one for children (<18 years) and one for adults (≥18 years) with epilepsy. The regression analysis included 65.5% (255/389) children with epilepsy and 57.5% (338/587) adults with epilepsy.

## 3. Results

### 3.1. Demographic information

The survey yielded 976 responses; with 60.1% of the overall sample involving adults with epilepsy, while the remaining were children with epilepsy (Table 1). Geographically, responses were from across Australia: New South Wales (38.5%), Queensland (22%), Victoria (15.2%), Western Australia (13.6%), and South Australia (4.5%), with the remainder forming 6.1%. Epilepsy syndrome of unknown type was the most frequently reported type of epilepsy across both children (41%) and adults (46%) with epilepsy (see Data S2). The second highest frequency syndrome type was structural brain abnormality (4.6%) in

[1] Using existing data collections in research: Guidelines for researchers 2014. The University of Sydney [29/10/16] Available from: https://intranet.sydney.edu.au/content/dam/intranet/documents/research-support/ethics/ethics-existing-data-guidelines.pdf

**Table 2**
Reported use and efficacy of cannabis products in children and adults with epilepsy.

| | Children with epilepsy | | | Adults with epilepsy | | |
|---|---|---|---|---|---|---|
| | History of medicinal cannabis use N (%) | No history of medicinal cannabis use N (%) | Missing (%) | History of medicinal cannabis use N (%) | No history of medicinal cannabis use N (%) | Missing (%) |
| | 51 (13.0) | 340 (87.0) | | 86 (15.0) | 502 (85.0) | |
| Perceived efficacy | 10 (19.6) | | | 6 (7.0) | | |
| Successful | 36 (70.6) | – | | 77 (89.5) | – | |
| Unsuccessful | 5 (9.8) | – | | 3 (3.5) | – | |
| Reduction in AEDs | 13 (25.6) | | | 14 (16.3) | | |
| Yes | 26 (50.9) | – | | 41 (47.7) | – | |
| No | 12 (23.5) | – | | 31 (36.0) | – | |
| | Mean (SD) | Mean (SD) | Missing (%) | Mean (SD) | Mean (SD) | Missing (%) |
| Duration of use (months) | 15.75 (15.65) | – | 47 (92.2) | 47.7 (117.3) | – | 77 (89.5) |
| Number of seizures per month | | 30.6 (196.4) | 169 (49.7) | | 30.8 (137.9) | 271 (53.9) |
| Prior to starting cannabis | 12.8 (16.7) | – | 43 (84.3) | 52.9 (90.48) | – | 73 (84.9) |
| After starting cannabis | 2.5 (73.2) | – | 45 (88.2) | 3.68 (8.7) | – | 78 (90.6) |

Note: Dash (—) indicates not applicable.

children with epilepsy, and temporal lobe epilepsy (5.6%) in adults with epilepsy.

### 3.2. Prevalence of medicinal cannabis use

Overall, 14% (137/976) of respondents reported currently using or having previously used cannabis products to treat epilepsy. Of the 389 children with epilepsy included in the survey, 13% (51) had a reported history of cannabis product use for epilepsy (Table 2). Of these, 71% (36/51) parents/guardians rated cannabis products as successful in helping them manage their child's seizures. Furthermore, 51% (26/51) parents/guardians reported reduced use of AEDS by their child after commencing use of cannabis products.

Of the 587 adults with epilepsy, 15% were currently using or had previously used cannabis-based products. In terms of perceived efficacy, 89.5% (77/86) adults with epilepsy reported cannabis products as successful in helping them to treat their epilepsy, and 47.7% (41/86) reported reducing their number of AEDs after commencing use of cannabis

**Table 3**
Predictors of a history of medicinal cannabis use in adults and children with epilepsy.

| | | | Univariate | | [b]Multivariate | |
|---|---|---|---|---|---|---|
| [a]Attribute | Children with history of medicinal cannabis use Mean (SD) | Children with no history of medicinal cannabis use Mean (SD) | Odds ratio (95% CI) | *p* value | Odds ratio (95% CI) | [#]*p* value |
| Past AEDs | **7.64 (5.9)** | **4.65 (4.3)** | **1.1 (1.06–1.18)** | **.0001** | **1.09 (1.04–1.17)** | **.002** |
| | **N (%)** | **N (%)** | | | | |
| Ketogenic diet | **12 (23.5)** | **31 (9.2)** | **3.1 (1.45–6.42)** | **.003** | **2.45 (1.09–1.17)** | **.031** |
| Simple partial seizures | **29 (56.9)** | **108 (32.0)** | **2.8 (1.54–5.11)** | **.001** | **2.17 (1.09–5.52)** | **.018** |
| Unknown type seizures | **15 (29.4)** | **40 (11.8)** | **3.1 (1.56–6.17)** | **.001** | **3.19 (1.53–6.66)** | **.002** |
| Tonic-clonic seizures | 44 (86.3) | 248 (73.4) | 2.3 (.99–5.25) | .052 | | NS |
| Tonic seizures | 23 (45.1) | 94 (27.3) | 2.1 (1.17–3.88) | .013 | | NS |
| Myoclonic jerks | 30 (58.8) | 138 (40.8) | 2.1 (1.14–3.77) | .017 | | NS |
| Epileptic spasms | 17 (33.3) | 61 (18.0) | 2.27 (1.19–4.32) | .013 | | NS |
| Absence seizures | 41 (80.4) | 214 (63.3) | 2.38 (1.15–4.9) | .019 | | NS |
| Complex partial seizures | 30 (58.8) | 148 (43.8) | 1.8 (1.01–3.33) | .047 | | NS |

| Attribute | Adults with history of medicinal cannabis use Mean (SD) | Adults with no history of medicinal cannabis use Mean (SD) | Odds ratio (95% CI) | *p* value | Odds ratio (95% CI) | [#]*p* value |
|---|---|---|---|---|---|---|
| Past AED | **6.44 (5.5)** | **4.5 (4.0)** | **1.1 (1.04–1.14)** | **<0.001** | **1.1 (1.04–1.16)** | **0.001** |
| | **N (%)** | **N (%)** | | | | |
| Structural cause epilepsy | **7 (29.2)** | **17 (70.8)** | **2.3 (0.921–5.91)** | **0.074** | **2.9 (1.08–7.83)** | **0.045** |
| Pain | **10 (17.2)** | **8 (3.5)** | **0.12 (0.047–0.322)** | **<0.001** | **6.1 (1.55–7.14)** | **0.009** |
| Other neurological conditions | **20 (34.5)** | **60 (26.0)** | **0.43 (0.245–0.751)** | **0.003** | **3.4 (1.66–1.04)** | **0.001** |
| Other medical conditions | 58 (67.4) | 231 (46.7) | 2.4 (1.45–3.86) | <0.001 | | NS |
| Myoclonic jerks | 35 (40.7) | 129 (25.7) | 0.51 (0.314–0.812) | 0.005 | | NS |
| Epileptic spasms | 13 (15.1) | 30 (6.0) | 0.36 (0.178–0.717) | 0.004 | | NS |
| Unknown seizure type | 21 (24.4) | 69 (13.8) | 0.49 (0.284–0.86) | 0.013 | | NS |

NS = not significant in multivariate analysis; AED = antiepileptic drug(s)
[a] Predictors tested: 34 variables, including seizure type, epilepsy syndrome, past and present number of antiepileptic drugs tried, presence of other medical conditions, and epilepsy treatment history.
[b] Including only those with variables $p < 0.1$ in univariate analysis.
[#] Significance set at $p < .05$ (significant variables in bold).

products. The majority of the cannabis products were obtained from illegal suppliers with no formal known composition aside from one adult with epilepsy who reported accessing their cannabis product through the Therapeutic Goods Administration (TGA) Special Access Scheme. Further information on cannabis product use for this group is summarized in Table 2.

### 3.3. Predictors associated with cannabis product use in people with epilepsy based on medical history

#### 3.3.1. Children with epilepsy

Based on the univariate analysis, the following predictors of cannabis extract use in children with epilepsy were chosen for inclusion in the multivariate model (i.e. all met the inclusion criteria of $p < 0.1$): past AEDs; ketogenic diet; simple partial seizures; unknown type seizures; tonic-clonic seizures; tonic seizures; myoclonic jerks; epileptic spasms; absence seizures; and complex partial seizures (Table 3). In the multivariate analysis, the number of AEDs tried in the past (odds ratio [OR] 1.1; 95% CI 1.04–1.17; $p = .002$) was a significant predictor of cannabis use as a treatment for the child's epilepsy. That is, with each additional AED tried in the past, parents/guardians were 1.1 times more likely to have tried cannabis as a treatment for their child's epilepsy. Current use of ketogenic diet was also a significant predictor of medicinal cannabis use ([OR] 2.45; 95% CI 1.09–1.17; $p = .031$) as was the presence of simple partial seizures ([OR] 2.17; 95% CI 1.09–5.52; $p = .018$) or unknown seizure types ([OR] 3.19; 95% CI 1.53–6.66; $p = .002$). No other variables were found to be significant predictors in the multivariate model.

#### 3.3.2. Adults with epilepsy

Based on the univariate analysis, the following predictors of medicinal cannabis use in adults with epilepsy were chosen for inclusion in the multivariate model (i.e. all met the inclusion criteria of $p < 0.1$): number of past AEDs used; presence of other medical conditions in addition to epilepsy; pain; presence of another neurological condition; structural cause of epilepsy; and presence of several seizure types (myoclonic jerks, epileptic spasms, and unknown seizure type) (Table 3). In the multivariate analysis, the number of past AEDs tried was a significant predictor of cannabis product use for the treatment of adult epilepsy ([OR] 1.1; 95% CI 1.04–1.16; $p = .001$), with each new AED trialled in the past resulting in a 1.1-fold greated likelihood of the individual trying cannabis products to treat their epilepsy. Adults who reported having a neurological condition (e.g. chronic migraine or acquired brain injury) in addition to epilepsy had a 3.4 times greater likelihood of having a history of cannabis product use compared to adults who did not report such conditions ([OR] 3.4; 95% CI 1.7–1.04; $p = .001$). Presence of pain in addition to epilepsy was also a significant predictor ([OR] 6.1; 95% CI 1.6–7.1; $p = .009$) as was epilepsy due to a structural brain abnormality ([OR] 2.9; 95% CI 1.1–7.8; $p = .045$).

### 3.4. Reasons for and against using cannabis products for epilepsy

Forty-five percent (39/86) of adults and 71% (36/51) of children were reported to have used cannabis products due to the treatment-resistant nature of their epilepsy. Sixteen percent (14/86) of adults and 22% (11/51) of children were reported to have used cannabis products in an attempt to find an alternative treatment due to experiencing intolerable side effects of conventional AEDs. For 21% of adults with epilepsy, cannabis was inadvertently assisting to manage seizures following recreational cannabis use experience. Seventy-one percent (353/502) of adults and 81% (274/340) of children with no history of cannabis product use for epilepsy reported difficulty accessing cannabis (such as issues with finding a reliable and consistent supply, current illegal status, lack of guidance and support from medical doctor, and financial strain) as the main reason for not trying cannabis products. The remaining reasons reported for using or not using cannabis products to manage epilepsy in children and adults are summarized in Table 4.

### 3.5. Reasons for and against participating in research trials

In response to the question, "Would you choose to participate in medicinal cannabis research trials?", 62% (240/389) of parents/guardians of children with epilepsy and 56% (327/587) of adults with epilepsy reported willingness to participate in a clinical trial of a cannabinoid treatment for epilepsy (Table 5). The main reasons for participating were not dissimilar to reasons for its use in the first place, that is, treatment-

**Table 4**
Themes identified for reasons for and against using cannabis products to manage epilepsy.

| | Children with epilepsy (%) | Missing (%) | | Adults with epilepsy (%) | Missing (%) |
|---|---|---|---|---|---|
| *Reasons for use of cannabis products for epilepsy* | | | | | |
| Treatment-resistant epilepsy | 36 (70.6) | 2 (3.9) | Treatment-resistant epilepsy | 39 (45.3) | 6 (7.0) |
| Unacceptable AED side-effects | 11 (21.6) | | Recreational use experience | 18 (20.9) | |
| Success stories (media) and word of mouth | 6 (11.8) | | To manage other health conditions (and epilepsy) | 15 (17.4) | |
| Recreational use experience | 0 | | Unacceptable AED side-effects | 14 (16.3) | |
| To manage other health conditions (and epilepsy) | 0 | | Success stories (media) and word of mouth | 12 (14.0) | |
| Personal research on cannabis products and epilepsy | 3 (5.9) | | Personal research on cannabis products and epilepsy | 9 (10.5) | |
| Recommendation by medical doctor | 3 (5.9) | | Recommendation by medical doctor | 6 (7.0) | |
| *Reasons against or hesitation towards use of cannabis products for epilepsy* | | | | | |
| Difficulties with access | 274 (81.1) | 36 (10.7) | Difficulties with access | 353 (70.5) | 51 (10.2) |
| Illegal status | 134 (39.6) | | Difficulties with sourcing reliable supply | 132 (26.3) | |
| Difficulties with sourcing reliable supply | 99 (29.3) | | Illegal status | 128 (25.5) | |
| Not offered or recommended by medical doctor | 36 (10.7) | | Not offered or recommended by medical doctor | 85 (17.0) | |
| Financial strain | 5 (1.5) | | Financial strain | 8 (1.6) | |
| Concerns over safety | 83 (24.6) | | Concerns over safety | 82 (16.4) | |
| Possible short- and long-term associated risks | 24 (7.1) | | Lacking information or support for its use | 29 (5.8) | |
| Need for medical supervision | 19 (5.6) | | Possible short- and long-term associated risks | 19 (4.2) | |
| Unsure of composition and dosage | 17 (5.0) | | Need for medical supervision | 14 (2.8) | |
| Lacking information or support for its use | 10 (3.0) | | Lack of evidence for its efficacy | 10 (2.0) | |
| Concerns over possible interactions with AEDs | 8 (2.4) | | Unsure of composition and dosage | 7 (1.4) | |
| Lack of evidence for its efficacy | 5 (1.5) | | Concerns over possible interactions with AEDs | 3 (0.6) | |
| Other reasons | 45 (13.3) | | Other reasons | 66 (13.2) | |
| Epilepsy currently controlled | 43 (12.7) | | Epilepsy currently controlled | 59 (11.8) | |
| Concerns over informed consent | 1 (0.3) | | Stigma | 5 (1.0) | |
| Stigma | 1 (0.3) | | Concerns over informed consent | 2 (0.4) | |

Note: Respondents able to provide more than one answer to the question. AED(s) = antiepileptic drug(s).

**Table 5**
Reasons for and against or hesitation towards participating in clinical trials for cannabinoids in children and adults with epilepsy.

| | Children (%) | Missing (%) | | Adults (%) | Missing (%) |
|---|---|---|---|---|---|
| Willing to participate in cannabinoid trials for epilepsy | 240 (61.7) | 30 (7.7) | | 327 (55.7) | 84 (14.3) |
| *Reasons for participation* | | | | | |
| Treatment-resistant epilepsy | 159 (66.3) | | Treatment-resistant epilepsy | 186 (56.9) | |
| Unacceptable AED side effects | 45 (18.8) | | Unacceptable AED side effects | 59 (21.9) | |
| Potentially safer ("natural") and more effective | 35 (14.6) | | Potentially safer ("natural") and more effective | 37 (11.3) | |
| To assist scientific research | 26 (10.8) | | To assist scientific research | 48 (14.7) | |
| To help create legal access and supply | 7 (2.9) | | To help create legal access and supply | 14 (5.2) | |
| To help manage other health conditions (and epilepsy) | 4 (1.7) | | To help manage other health conditions (and epilepsy) | 8 (3.0) | |
| To decriminalize its use (medicinal purposes) | 3 (1.3) | | To decriminalize its use (medicinal purposes) | 1 (0.3) | |
| To reduce the cost of the cannabis product | 2 (0.8) | | To reduce the cost of the cannabis product | 1 (0.3) | |
| Against or hesitation towards participating in trials | 119 (30.6) | | | 176 (30.0) | |
| Reasons against or hesitation towards participation | | 42 (35.3) | | | 109 (61.9) |
| Concerns over safety | 38 (31.9) | | Concerns over safety | 56 (31.8) | |
| Possible short- and long-term associated risks | 19 (16.0) | | Possible short- and long-term associated risks | 26 (14.7) | |
| Risk worsening current state (by transitioning medication) | 14 (11.8) | | Risk worsening current state (by transitioning medication) | 22 (12.5) | |
| Require medical doctor's recommendation | 5 (4.2) | | Require medical doctor's recommendation | 5 (2.8) | |
| Age (too young) | 1 (0.8) | | Drug interactions (AEDs and other medications) | 3 (1.7) | |
| Concerns over clinical trial design | 31 (26.1) | | Require additional information | 32 18.2) | |
| Dislike of isolated/synthetic compounds | 12 (10.1) | | Uncertainty over suitability for trial | 16 (9.1) | |
| Risk being allocated placebo | 14 (11.8) | | Need more information to make decision | 11 (6.3) | |
| Trial dose not tailored to individual | 4 (3.4) | | Unsure of its effectiveness for specific epilepsy conditions | 5 (2.8) | |
| Require additional information | 35 (29.4) | | Concerns over clinical trial design | 9 (5.1) | |
| Need more information to make decision | 19 (16.0) | | Dislike of isolated/synthetic compounds | 2 (1.2) | |
| Uncertainty over suitability for trial | 11 (9.2) | | Trial dose not tailored to individual | 3 (1.7) | |
| Unsure of its effectiveness for specific epilepsy conditions | 5 (4.2) | | Age (i.e. exclusion of older adults) | 2 (1.2) | |
| Other reasons | 11 (9.2) | | Risk being allocated placebo | 2 (1.2) | |
| Epilepsy currently well-controlled | 10 (8.4) | | Other reasons | 29 (16.5) | |
| Trials unnecessary as scientific evidence already available | 1 (0.8) | | Epilepsy currently well controlled | 20 (11.4) | |
| Stigma | 0 (0.0) | | Stigma | 5 (2.8) | |
| | | | Illegal status | 3 (1.7) | |
| | | | Trials unnecessary as scientific evidence already available | 1 (0.6) | |

Note: Respondents able to provide more than one answer to the question. AED(s) = antiepileptic drug(s).

resistant epilepsy and dissatisfaction with side-effect profile of AEDs. The main overarching theme for not wanting to participate in a clinical trial was concerns over its safety and tolerability in children (32%) and adults (32%) with epilepsy. Table 6 summarizes the survey respondents' remaining reasons for and against participating in clinical trials for cannabinoids in epilepsy.

**Table 6**
Total number and percentage of preference of cannabis product and access to cannabis product for children and adults with epilepsy.

| | Children with epilepsy (%) | Missing (%) | Adults with epilepsy (%) | Missing (%) |
|---|---|---|---|---|
| *Preferred cannabis product* | | | | |
| I do not know | 246 (63.2) | 30 (7.7) | 354 (60.3) | 84 (14.3) |
| Botanical whole plant compounds | 69 (17.7) | | 96 (16.4) | |
| Combination of botanical compounds | 17 (4.4) | | 26 (4.4) | |
| Single botanical compound | 19 (4.9) | | 15 (2.6) | |
| Synthetic compound | 8 (2.1) | | 12 (2.0) | |
| *Preferred access and supply* | | | | |
| Known medicinal cannabis product supplier | 212 (54.5) | | 226 (38.5) | |
| Undecided | 107 (27.5) | | 156 (26.6) | |
| Pharmaceutical product | 98 (25.2) | | 145 (24.7) | |
| Grow and/or make your own | 42 (10.8) | | 114 (19.4) | |
| Co-operative group or club | 39 (10.) | | 62 (10.6) | |
| Overseas legal commercial product source | 35 (9.0) | | 29 (4.9) | |
| Local recreational supplier (raw form) | 19 (4.9) | | 77 (13.1) | |
| Internet-sourced product | 11 (2.8) | | 29 (4.9) | |

Note: Respondents able to choose more than one option to the question relating to preferred access and supply.

### 3.6. Preference of cannabis product type and accessibility

In response to the question, "What is your preferred cannabis product?" 63% of parents/guardians of children with epilepsy and 60% of adults with epilepsy responded with "I do not know". The second preference for parents/guardians of children with epilepsy and adults with epilepsy was botanical whole plant compounds (17.7% and 16.4%, respectively). In terms of access and supply of the cannabis product, the main preference in 54.5% (212/389) of parents/guardians of children and 38.5% (226/587) of adults with epilepsy was obtaining the cannabis product from a known medicinal cannabis product supplier. Table 6 summarizes the remaining preferences for cannabis products and access and supply of cannabis products across children and adults with epilepsy.

## 4. Discussion

Overall, this Australian nationwide survey indicated that 13% of children and 15% of adults with epilepsy are currently using or have previously used cannabis products to treat epilepsy. The survey findings indicate that both parents/guardians of children and adults who have used cannabis extracts for epilepsy report a high level of perceived efficacy with cannabis products and that people with epilepsy in the Australian community are eager to engage in and assist with future research into cannabinoid medicine. Just under half of the respondents with a history of cannabis product use also reported reducing the number of AEDs after commencing use of cannabis products. The number of past AEDs tried was a significant predictor of cannabis product use in both adults and children with epilepsy. Consistent with this, treatment-resistant epilepsy and dissatisfaction with the side effects of conventional AEDs were the two main reasons for using cannabis

products across all survey respondents. Adults with a neurological or pain condition in addition to epilepsy were significantly more likely to have tried cannabis products. Major barriers to using cannabinoids included difficulties with accessing cannabis products and concerns over its safety. The willingness to participate in clinical trials for cannabinoid treatment of epilepsy related to the aims of identifying a safer and more effective alternative to AEDs and to assisting with scientific research. The main reason for not participating involved concerns over safety of use.

Given that the likelihood of "sustained" seizure-freedom decreases and side effects tend to increase with each new combination of AEDs, it is reasonable that people with epilepsy, particularly those whose seizures are treatment-resistant, are pursuing alternative treatments to manage seizures. Adverse side effects of antiepileptic polypharmacy impose restrictions on the quality of life in people with active epilepsy [33, 34]. A patient survey at a tertiary epilepsy center indicated that the psychiatric side effects of AEDs (depressed mood, irritability, aggression) were the least well-tolerated by patients with epilepsy, followed by cognitive and physiological side effects [35]. Physical side effects, such as weight gain and tiredness, were better tolerated but still imposed a considerable burden. In this survey, just under 50% of all users reported to have decreased some of their AEDs after commencing cannabis products.

Adults with epilepsy, but not parents of children with epilepsy, indicated that recreational use of cannabis had fortuitously assisted in managing seizures. No parent or guardian reported using cannabis products to manage their child's other medical conditions. In contrast, adults with epilepsy indicated that cannabis assisted in managing other cognitive, neurological, physical, and/or mental health conditions. Interestingly, adults who had reported having pain (e.g. chronic pain, migraines) or other neurological condition in addition to epilepsy were more likely to have tried cannabis products. Sexton and colleagues' survey indicated that pain was the most frequently reported condition for which medicinal cannabis was being used, and that cannabis users reported to experience substantial symptom relief [28].

The survey indicated that the majority of respondents wanted to participate in a clinical trial for cannabis-based treatment for epilepsy, with the main reasons similar to those underlying it use; i.e., better management of drug-resistant epilepsy and reduced side effects relative to AEDs. Respondents also expressed interest in wanting to assist with the scientific research, and to find an alternative treatment that is "natural" and therefore safer and more effective. The latter may reflect the naturalistic fallacy, that is, the belief that nature's produce is intrinsically safe [2]. Indeed, both adults and parents of children with epilepsy most preferred a botanical whole plant compound, with preference for synthetic compounds forming the minority (2.3%).

The uncertainty over the possibility of short- and long-term side effects of cannabinoid use emerged as one of the main reasons against trying cannabis products or participating in cannabinoid research trials. Preliminary findings from an open-label clinical trial of plant-derived CBD (Epidiolex™) in children with severe epilepsy indicated an adequate safety profile, with only 3% (5/162) of patients discontinuing treatment due to an adverse event despite 12% (14/162) experiencing a serious adverse event [22]. Future studies with a control group of severe epilepsy types are necessary to determine the rate of CBD-related adverse events following short-term and long-term administration. In the current survey, only a small proportion of people with epilepsy (6.5%) reported using cannabis products following recommendation by their medical doctor (neurologist or epileptologist). This reflects findings from a recent online survey, which indicated that fewer medical specialists support its use as compared to general medical personnel, patients, and the public [36]. It is important to note that many locally sourced artisanal cannabis products may contain other cannabinoids, of which the safety profile is currently unknown, along with possible contaminants such as heavy metals, pesticides, bacteria, and molds.

Another concern that both adults and parents/guardians of children with epilepsy identified was the risk of worsening seizure activity by transitioning onto a new medication. Al-Kattan and colleagues identified that missed doses of AEDs was the most frequent precipitating factor for a breakthrough seizure (56.4%), followed by sleep deprivation (36.4%) and psychological stress (34.5%) [37]. Other factors include drug-drug interactions whereby the blood concentrations of the affected drug is decreased, resulting in a breakthrough seizure [38]. Cannabinoids such as CBD can have complex pharmacokinetic interactions with other drugs, including AEDs, but more in the direction of augmenting of AEDs (e.g. clobazam) via inhibition of specific CYP450 enzymes [39]. This may act to improve seizure control, albeit with the potential cost of increasing AED side effects [40]. It would appear important that such information on AED interactions is provided to the community, given the likely increased interest in, and adoption of, cannabis-based therapies.

Naturally, there are intrinsic limitations to an anonymous open-access online survey such as the current one, and this prevents any assertions regarding the overall efficacy of cannabis-based products being used in the community. This includes potential for multiple responses for a single individual (e.g. two parents responding for the same child), lack of clinician confirmation of epilepsy, and participation bias. It is possible that individuals who benefitted from cannabis products were more likely to complete the survey versus those who did not experience any benefits, resulting in a potentially unrepresentative sample. The retrospective nature of parent self-report, which is prone to poor recollection and expectation bias, is also problematic. In a recent survey, families who relocated to Colorado to access legal medicinal cannabis were three times as likely to report a >50% seizure reduction than families with established healthcare in the state [24]. This suggests a strong placebo effect, which can amplify parent perceptions of the cannabis product's therapeutic effect.

Moreover, artisanal cannabis products are of uncertain quality and may contain different cannabinoids of varying concentration, and with any number of possible contaminants [41]. A recent study showed that a large proportion of edible cannabis products (baked food, beverages, and confectionary), sold in three major cities within the United States, failed to meet basic label accuracy standards for pharmaceuticals [42]. With regards to tetrahydrocannabinol (THC) content, 60% of products had significantly less cannabinoid content than stated on the label, which calls into question whether such products would result in any therapeutic benefit. The present survey did not specifically probe the type of cannabis products being used (e.g. raw form or an extracted preparation), how they were obtained or how they were being administered (e.g. smoked or ingested in oil form), precluding more detailed insight into the range of products being used within the community. Given the lack of regulation and quality assurance of artisanal cannabis products in the community, objective evaluation of standardized cannabis-based extracts is clearly warranted to relate efficacy, safety, and tolerability of these products to cannabinoid dose and concentration.

Despite these issues, what is clear is that we cannot ignore that a significant proportion of children and adults with epilepsy are using cannabis-based products in Australia, and that a high proportion of these people are reporting considerable benefit to their condition. Furthermore, a substantial proportion of respondents also reported reducing their use of AEDs after commencing cannabis products. While this may be due to a reduced requirement for AEDs to manage their condition due to positive effects of the cannabis product, it is concerning if this medication change is undertaken without close medical supervision. Given their prevalence of use identified in the present study, this possibility highlights the growing need to educate key patient groups on cannabis-based products and, in particular, to encourage patients to ensure they seek medical advice before making any major changes to their treatment regimen. Fortunately, preliminary findings from clinical trials examining the safety and efficacy of CBD are promising [21,

22], particularly for those with treatment-resistant epilepsies, but also for those with treatment-responsive epilepsy seeking a better side effect profile relative to conventional AEDs. However, further studies are necessary to increase our knowledge of the efficacy, interaction effects, and safety of CBD, and to explore the potential role of other cannabinoids, either alone or in combination, in the treatment of epilepsy.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2017.02.005.

## Disclosures of conflicts of interest

None of the authors has any conflict of interest to disclose.

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## References

[1] Kwan P, Brodie MJ. Neuropsychological effects of epilepsy and antiepileptic drugs. Lancet 2001;357(9251):216–22.
[2] Friedman D, Devinsky O. Cannabinoids in the treatment of epilepsy. N Engl J Med 2015;373(11):1048–58.
[3] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51(6):1069–77.
[4] Brodie M, Barry S, Bamagous G, Norrie J, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. Neurology 2012;78(20):1548–54.
[5] Sperling MR. The consequences of uncontrolled epilepsy. CNS Spectr 2004;9(02):98–109.
[6] Elliott IM, Lach L, Smith ML. I just want to be normal: a qualitative study exploring how children and adolescents view the impact of intractable epilepsy on their quality of life. Epilepsy Behav 2005;7(4):664–78.
[7] De Boer HM, Mula M, Sander JW. The global burden and stigma of epilepsy. Epilepsy Behav 2008;12(4):540–6.
[8] Gillham R, Baker G, Thompson P, Birbeck K, McGuire A, Tomlinson L, et al. Standardisation of a self-report questionnaire for use in evaluating cognitive, affective and behavioural side-effects of anti-epileptic drug treatments. Epilepsy Res 1996;24(1):47–55.
[9] Marsicano G, Goodenough S, Monory K, Hermann H, Eder M, Cannich A, et al. CB1 cannabinoid receptors and on-demand defense against excitotoxicity. Science 2003;302(5642):84–8.
[10] Soltesz I, Alger BE, Kano M, Lee S-H, Lovinger DM, Ohno-Shosaku T, et al. Weeding out bad waves: towards selective cannabinoid circuit control in epilepsy. Nat Rev Neurosci 2015;16(5):264–77.
[11] Katona I. Cannabis and endocannabinoid signaling in epilepsy. Endocannabinoids. Springer; 2015. p. 285–316.
[12] Ludányi A, Erőss L, Czirják S, Vajda J, Halász P, Watanabe M, et al. Downregulation of the CB1 cannabinoid receptor and related molecular elements of the endocannabinoid system in epileptic human hippocampus. J Neurosci 2008;28(12):2976–90.
[13] Satta V, Rubio M, Valdeolivas S, Piscitelli F, Verde R, Barroso E, et al. Possible dysregulation of the endocannabinoid system in a cohort of patients with Dravet syndrome. Eur Neuropsychopharmacol 2016;26:S251.
[14] Iannotti FA, Hill CL, Leo A, Alhusaini A, Soubrane C, Mazzarella E, et al. Nonpsychotropic plant cannabinoids, cannabidivarin (CBDV) and cannabidiol (CBD), activate and desensitize transient receptor potential vanilloid 1 (TRPV1) channels in vitro: potential for the treatment of neuronal hyperexcitability. ACS Chem Nerosci 2014;5(11):1131–41.
[15] Carletti F, Gambino G, Rizzo V, Ferraro G, Sardo P. Involvement of TRPV1 channels in the activity of the cannabinoid WIN 55,212-2 in an acute rat model of temporal lobe epilepsy. Epilepsy Res 2016;122:56–65.
[16] Golovko T, Min R, Lozovaya N, Falconer C, Yatsenko N, Tsintsadze T, et al. Control of inhibition by the direct action of cannabinoids on GABAA receptors. Cereb Cortex 2014:bhu045.
[17] Pertwee RG. Handbook of cannabis. USA: Oxford University Press; 2014.
[18] Maa E, Figi P. The case for medical marijuana in epilepsy. Epilepsia 2014;55(6):783–6.
[19] Koppel BS, Brust JC, Fife T, Bronstein J, Youssof S, Gronseth G, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2014;82(17):1556–63.
[20] Gloss D, Vickrey B. Cannabinoids for epilepsy. Cochrane Libr; 2014.
[21] Hess EJ, Moody KA, Geffrey AL, Pollack SF, Skirvin LA, Bruno PL, et al. Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex. Epilepsia 2016;57(10):1617–24.
[22] Devinsky O, Marsh E, Friedman D, Thiele E, Laux L, Sullivan J, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol 2016;15(3):270–8.
[23] Tzadok M, Uliel-Siboni S, Linder I, Kramer U, Epstein O, Menascu S, et al. CBD-enriched medical cannabis for intractable pediatric epilepsy: the current Israeli experience. Seizure 2016;35:41–4.
[24] Press CA, Knupp KG, Chapman KE. Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. Epilepsy Behav 2015;45:49–52.
[25] Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. Epilepsy Behav 2013;29(3):574–7.
[26] Treatment with CBD in oily solution of drug-resistant paediatric epilepsies. In: Pellicia A, Grassi G, Romano A, Crocchialo P, editors. Congress on cannabis and the cannabinoids. Leiden, The Netherlands: International Association for Cannabis as Medicine; 2005.
[27] Hussain SA, Zhou R, Jacobson C, Weng J, Cheng E, Lay J, et al. Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: a potential role for infantile spasms and Lennox–Gastaut syndrome. Epilepsy Behav 2015;47:138–41.
[28] Sexton M, Cuttler C, Finnell JS, Mischley LK. A cross-sectional survey of medical cannabis users: patterns of use and perceived efficacy. Cannabis Cannabinoid Res 2016;1(1):131–8.
[29] Lee J. Senate passes medicinal cannabis legislation Sydney Morning Herald — federal politics. [23/12/16]. Available from: http://www.smh.com.au/federal-politics/political-news/senate-passes-medicinal-cannabis-legislation-20160224-gn2gjk.html; 2016.
[30] Aubusson K. The little girl behind Lamberts' $30 million donation for medicinal cannabis research. Sydney Morning Herald; 2015 [23/12/16]. Available from: http://www.smh.com.au/nsw/the-little-girl-behind-lamberts-30-million-donation-for-medicinal-cannabis-research-20150612-ghmzfu.html.
[31] Weinstein JN, Lurie JD, Tosteson TD, Hanscom B, Tosteson AN, Blood EA, et al. Surgical versus nonsurgical treatment for lumbar degenerative spondylolisthesis. N Engl J Med 2007;356(22):2257–70.
[32] Arif H, Buchsbaum R, Weintraub D, Koyfman S, Salas-Humara C, Bazil C, et al. Comparison and predictors of rash associated with 15 antiepileptic drugs. Neurology 2007;68(20):1701–9.
[33] Gilliam F. Optimizing health outcomes in active epilepsy. Neurology 2002;58(8 Suppl. 5):S9–20.
[34] de Kinderen RJ, Evers SM, Rinkens R, Postulart D, Vader CI, Majoie MH, et al. Side-effects of antiepileptic drugs: the economic burden. Seizure 2014;23(3):184–90.
[35] Witt J-A, Elger CE, Helmstaedter C. Which drug-induced side effects would be tolerated in the prospect of seizure control? Epilepsy Behav 2013;29(1):141–3.
[36] Mathern GW, Beninsig L, Nehlig A. Fewer specialists support using medical marijuana and CBD in treating epilepsy patients compared with other medical professionals and patients: result of Epilepsia's survey. Epilepsia 2015;56(1):1–6.
[37] Al-Kattan M, Afifi L, Shamloul R, Mostafa EED. Assessment of precipitating factors of breakthrough seizures in epileptic patients. Egypt J Neurol Psychiatry Neurosurg 2015;52(3):165.
[38] Besag F, Patsalos PN. Clinically important antiepileptic drug interactions and their influence on adverse effects in epilepsy. In: St Louis EK, Ficker DM, editors. Epilepsy and the interictal state: comorbidities and quality of life. Wiley-Blackwell; 2015. p. 110–9.
[39] Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia 2015;56(8):1246–51.
[40] Devinsky O, Cilio MR, Cross H, Fernandez-Ruiz J, French J, Hill C, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia 2014;55(6):791–802.
[41] 2016 warning letters and test results for cannabidiol-related products [online article]. U.S. Food & Drug Administration; 2016[updated 08/31/2016 13/12/16]. Available from: http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm484109.htm.
[42] Vandrey R, Raber JC, Raber ME, Douglass B, Miller C, Bonn-Miller MO. Cannabinoid dose and label accuracy in edible medical cannabis products. JAMA 2015;313(24):2491–3.