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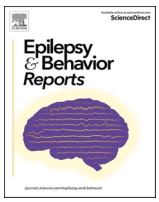

Clinician Understanding, Acceptance and utilization of Ketogenic diet therapy for epilepsy in Australia and New Zealand: An online survey

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ABSTRACT

Ketogenic diet therapy (KDT) is an established treatment for people with epilepsy. As increasing evidence demonstrates effectiveness and safety of KDT on seizure reduction, cognition and behaviour, it is essential to evaluate factors hindering and supporting neurologists in prescribing KDT to strengthen quality, evidence-based, appropriate and equitable care. A study of Australian and New Zealand (ANZ) neurologists was undertaken via an online survey. Demographics, clinical role characteristics, perceptions of knowledge, use and experiences of KDT for epilepsy treatment were assessed. Responses were analysed using the Capability, Opportunity, Motivation and Behaviour (COM-B) model. 114 neurologists participated (18 % response rate). All were aware of KDT for epilepsy treatment, most (90 %) perceived it as acceptable and 85 % identified suitable patients in their practice. Poor knowledge of the KDT referral processes was a barrier for 64 %. Clinical role characteristics were significantly associated with perceived level of knowledge and use of KDT in practice, being more likely among paediatric neurologists), epileptologists and those in urban practices ($p < 0.00001$). Most neurologists (90 %) endorsed adoption of a KDT guideline to facilitate use of KDT in epilepsy management. This study established that KDT is accepted as a suitable treatment for epilepsy in ANZ. There is high variability in perceived knowledge and skills related to KDT, which impacts on utilization in clinical practice. Further education and resources for clinicians, allied health and community support agencies are needed to optimise the use of this valuable therapy. Additionally, a clear referral pathway would improve patient access.

1. Introduction

Epilepsy is one the most common neurological conditions across all age groups and affects more than 70 million people worldwide and approximately 250,000 people in Australia [2,3]. Despite increasing medications available, up to a third of people have drug resistant epilepsy [4]. This is defined as ongoing seizures after the adequate trial of two tolerated, appropriately chosen and used antiseizure drug schedules (monotherapies or in combination) to achieve sustained seizure freedom [5]. Ongoing seizures have a significant impact on quality of life, mood, functional outcome and loss of productivity, as well as morbidity and mortality [6].

Ketogenic diet therapy (KDT), high-fat, low carbohydrate and protein diets, may be considered for treating people with drug resistant epilepsy. There are multiple potential mechanisms of action of KDT in epilepsy, including roles in the modulation of brain energy metabolism, ion channels, neurotransmitters, and oxidate stress, impacts on the gut microbiome, and epigenetic effects on methylation, histone modification and gene expression [7]. The multimodal approach of the KDT has advantages over anti-seizure medications alone which act predominantly by single mechanisms, such as sodium channels. and are reliant on individual people with epilepsy being sensitive to the same pathway modifications. KDT, when effective, can result in medication reduction and in some cases seizure freedom. A 2020 Cochrane review of evidence evaluated the effectiveness of KDT in children with drug resistant epilepsy compared to usual care and found that KDT may be up to three

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times more likely to achieve seizure freedom and up to six times more likely to experience a > 50 % reduction in seizure frequency [8]. In contrast, evidence in adults was uncertain and limited to two studies of 141 participants with drug resistant epilepsy that demonstrated adults may be up to five times more likely to experience a > 50 % reduction in seizure frequency on KDT. Subsequent clinical studies have established additional evidence for the effectiveness of KDT for adults with drug resistant epilepsy [9,10] and described increasing use of KDT [11]. When compared with seizure freedom rates in patients trialling their 3rd antiseizure medication (4.4 %) KDT appears to be more effective (13 %) [4,12]. In people with status epilepticus and refractory status epilepticus, KDT is effective, resulting in cessation of seizures in 63 % of patients with an additional 26 % of people achieving 50–99 % seizure reduction, even if introduced more than 3 months after onset [13].

However, there are challenges with use of KDT in people with drug resistant epilepsy, including long term adherence, side effects and compliance issues [14]. From a clinical practice perspective, differences in assessment, screening and monitoring practices have also been described in an international survey of 20 medical institutions [15]. In Australia and New Zealand (ANZ) KDT is provided by 12 centres, including 3 adult services in Australia and 9 paediatric in ANZ. The key factors influencing use, challenges and concerns in ANZ are unexplored. We hypothesise that clinicians will have a high interest in using KDT for drug resistant epilepsy, however utilisation is mismatched and there are further differences between paediatric and adult, metropolitan and regional healthcare practices. We predict this is, at least in part, due to the more extensive experience and evidence around the role of KDT in paediatric practice as well as differences in education and knowledge of the role of KDT between these groups.

To promote the uptake of evidence based KDT for drug resistant epilepsy in ANZ we used an implementation science theory-based implementation framework in the form of the Capability, Opportunity, Motivation and Behaviour (COM-B) Model [1] to explore, identify and understand neurologists' behaviours and practices that influence use of KDT. This model suggests our capability, opportunity and motivation determine behaviour. The COM-B can be used to identify interventions that modify one or more of these factors. Consequently, our objective in the present study was to gain insight into current perceptions, knowledge of KDT use and opinions regarding benefits, and barriers, to inform the development of strategies to strengthen the provision of timely and appropriately resourced KDT as part of best practice.

2. Methods

2.1. Design and participants

Adopting a cross-sectional design, neurologists currently involved in providing care to people with epilepsy in ANZ were eligible and invited to participate in the survey. Adult or paediatric neurologists not currently practicing in ANZ and trainee members were excluded. The study was approved by the Sydney Children's Hospital Network Human Research Ethics Committee (Ethics Approval Number 2022/PID006898-2022/ETH00623).

2.2. Recruitment

Recruitment opened on 31 August 2022 and closed 25 November 2022. Potential participants were identified through their local Neurological societies; Australian and New Zealand Association of Neurologists (ANZAN) and the Australia and New Zealand Child Neurology Society (ANZCNS). An invitation, study information sheet and link to the online survey hosted by Survey Monkey was emailed to all eligible clinicians. No reminder alerts were performed as per the societies' policies. Implied consent was obtained when the clinician chose to submit the survey. There was no financial compensation for clinicians participating in the study.

2.3. Data collection

The survey included 25-multiple choice questions (Appendix 1) developed based on the COM-B model [1] and rigorous piloting. The questionnaire included basic demographics (age, sex, clinical experience, region of practice and patient cohort seen). Four-point Likert scales, multiple choice, and short answer questions explored knowledge and understanding of KDT, the ability to access and refer patients for KDT consideration and perceived barriers to KDT implementation for clinicians and their patients with epilepsy. Questions were also developed to explore neurologist's interest in the development of a KDT guideline which would enable neurologists to offer this therapy in their local neurology centre for cases of SE or RSE or for patients who are on KDT in the community and require admission to hospital.

2.4. Data analysis

Quantitative data was analysed using descriptive statistics and graphs in IBM SPSS Statistics v26. Frequencies, percentages and ranges were reported for categorical variables. Chi squared analysis was used to compare characteristics of study participants and eligible non-participants for factors that were available (e.g., state of practice and practice location [16,17]. Chi-squared analysis or Fisher exact tests were performed to assess the relationship between region of practice (metropolitan and regional/rural) as well as speciality (Paediatrics/Adults). The threshold for statistical significance was set at $p < 0.05$.

3. Results

3.1. Demographic characteristics

Of the 641 neurologists identified, 114 initiated the survey, yielding a response rate of 18 %. All participants completed at least 75 % of the survey. There was a wide range of subspecialties, experience, and practice locations (Table 1). The percentage of responders from each practice region resembled the number of practicing Neurologists in each region with the largest responses coming from New South Wales, Victoria, Queensland and Western Australia. There were no differences between participants and eligible non-participants in terms of primary state of practice ($p = 0.07$, or area or practice ($p = 0.1$).

Almost half of the neurologists surveyed (49/114, 43 %) currently managed people with epilepsy and prescribed KDT, and some (15/114, 13 %) also managed patients with KDT for other indications. Among

Table 1
Sample demographics.

Characteristics Role	Neurologist (n = 114)
Adult General Neurologist	74 (65 %)
Adult Epileptologist	21 (19 %)
Paediatric General Neurologist	12 (10 %)
Paediatric Epileptologist	7 (6 %)
Clinical experience	
<3 years	18 (15 %)
3–10 years	36 (31 %)
>10 years	61 (54 %)
Practice location	
Metropolitan	82 (72 %)
Regional/Rural	16 (14 %)
Mixed	16 (14 %)
Australian Capital Territory	0 (0 %)
Queensland	12 (11 %)
New South Wales	61 (54 %)
Northern Territory	0 (0 %)
New Zealand	5 (4 %)
South Australia	7 (6 %)
Tasmania	5 (4 %)
Victoria	15 (13 %)
Western Australia	8 (7 %)

these neurologists, approximately half (27/49, 55 %) implemented KDT in their practice and others (22/49, 45 %) referred patients to specialist services for shared care. People with epilepsy were managed across a range of healthcare arrangements, including general neurology clinics, first seizure clinics and specialised complex epilepsy services that included advanced therapies such as KDT, epilepsy surgery and vagus nerve stimulation (Table 2).

3.2. Capability and experience with KDT

All neurologists were aware of KDT and most (103/114, 90 %) perceived it as an acceptable therapy for people with epilepsy. The majority (61/114, 71 %) were currently seeing at least five patients with drug resistant epilepsy and most (97/114, 85 %) identified at least one patient in their practice they felt would be suitable for a trial of KDT. Almost one quarter of neurologists (27/114, 24 %) reported 'strong' knowledge of KDT for epilepsy and utilised it in their practice. Another fifth (22/114, 19 %) described 'good' knowledge, however had no capacity to prescribe KDT in practice. Over half (65/114, 57 %) reported that their own knowledge limitations around KDT impacted their referrals for this therapy and likewise (46/114, 40 %) their patient's ability to access this therapy.

Neurologists' perceived knowledge regarding use and appropriate patient selection for KDT in drug resistant epilepsy varied (Fig. 1). While some (49/114, 43 %) reported they would not use KDT as first line therapy, others considered KDT as appropriate in this context for specific conditions, including glucose transporter type 1 deficiency syndrome (GLUT-1 DS), mitochondrial disorders and some genetic generalised epilepsies.

Awareness of the role of KDT in the management of status epilepticus was mixed, with some (49/114, 43 %) not currently considering use. One fifth (23/114, 20 %) reported their potential use of KDT in the first 72 h of status epilepticus and this increased after 72 h (60/114, 53 %).

3.3. Opportunity and motivation

Almost all neurologists (109/114, 96 %) felt that the challenging compliance for patients on KDT was a dissuading referral factor. Closely connected limiting factors endorsed by most neurologists were the restrictiveness of KDT and its impact on family meal planning and social outings (99/114, 87 %), with more than half (70/114, 61 %) indicating that these concerns adversely affected their patient referrals for this therapy. The impact of KDT on patients' overall health was also reported as a concern by more than one third of neurologists (43/114, 38 %), but for most (103/114, 90 %) this would not prevent KDT referral. For people with epilepsy controlled on medical therapy, most neurologists (88/114, 77 %) reported they would facilitate referral to the KDT clinic if requested by their patient.

Table 2
Healthcare Practice characteristics for neurologists managing people with drug resistant epilepsy.

Practice characteristics	n = 114
Public Hospital	57 (50 %)
Private Practice	7 (6 %)
Mixed Practice	50 (44 %)
Seizure clinic services	
Complex epilepsy service	54 (47 %)
First seizure/Epilepsy clinic	21 (18 %)
General Neurology clinic	39 (34 %)
Number of medically refractory epilepsy cases managed	
>50 patients	38 (33 %)
20–49 patients	20 (18 %)
5–19 patients	23 (20 %)
<5 patients	33 (29 %)

Additional common perceived barriers to the use of KDT among neurologists related to resource and cost challenges. These included difficulties in accessing specialist KDT services due to lack of awareness of referral pathways (84/114, 74 %), inability to refer patients to a public specialist epilepsy clinic providing KDT (36/114, 32 %), cost in private practice (32/114, 28 %), the extent of time managing patients on KDT (31/114, 27 %), and the cost of food and resources (9/114, 8 %).

Despite this, most (103/114, 90 %) indicated willingness to refer people with drug resistant epilepsy to a KDT service and some (30/114, 26 %) had more than 6 patients they were interested in referring. Almost all (105/114, 92 %) neurologists indicated interest in co-managing their patients with a multidisciplinary KDT team and none were concerned about losing involvement in their patients care.

Over half of neurologists (63/114, 55 %) indicated that they would refer more patients if there was better evidence regarding the outcomes of KDT in adolescents and adults with drug resistant epilepsy.

Most neurologists felt a well-defined referral pathway would increase their referrals for KDT (73/114, 64 %) and supported development and implementation of an ANZ KDT guideline (91/114, 80 %) that included monitoring, use in status epilepticus and management of complications. For patients in status epilepticus, most neurologists (90/114, 79 %) were willing to utilise a guideline for KDT, while others (20/114, 87 %) endorsed transfer to a specialised centre, and some (3/114, 3 %) perceived no role for KDT.

3.4. Sub analysis of paediatric and adult neurologists

Comparing perceptions and knowledge of KDT, paediatric neurologists were significantly more likely to understand current referral pathways (Paediatrics 18/19, Adult neurologists 38/95 40 %, P<0.00001) (Fig. 2).

Paediatric neurologists were more likely to have good/excellent knowledge of KDT (paediatric 19 /19, 95 %; adult 38/95, 40 %, $p < 0.00001$) and to prescribe it in their own clinical practice (paediatric 15/19, 79 %; adult 12/95, 13 %, $p < 0.00001$)) or refer patients to the local KDT service for KDT therapy (paediatric 19/19, 100 %; adult 30/95,32 %, $p < 0.00001$). Compared to adult neurologists, paediatric neurologists were also more likely to understand (paediatric 19/19,95 %; adult 38/95, 40 %, $p < 0.00001$) and be satisfied with current referral pathways (paediatric14/19, 74 %; adult 28/95, 29 %, $p < 0.05$) (Table 3). Most adult neurologists (67/95, 71 %) felt development of clear clinical guidelines would increase their referrals for KDT therapy.

Most adult responders felt better evidence around the use of KDT in adolescent and adult patients was needed to improve their referrals unlike paediatric responders who felt the current evidence base was strong (paediatric 1/19, 5 %), adult 62/95, 65 %, $p < 0.00001$). For people in status epilepticus all paediatric responders felt there was a role for KDT compared almost two thirds of the adult responders (paediatric 19/19, 100 %; adults 59/95, 62 %; $p < 0.00001$).

3.5. Sub analysis of metropolitan vs regional/rural clinicians

The frequency of KDT use and knowledge of referral pathways among clinicians for people living in regional, rural and remote areas was significantly lower than in metropolitan areas (regional/rural 1/16, 6 %; 47/98 48 %; $p < 0.00001$). Most regional/rural neurologists did not know how to refer an adolescent or adult patient to their local KDT service (regional/rural 15/16, 94 %; Metropolitan 59/98, 60 %; $p < 0.00001$). No neurologist in regional/rural areas had patients currently utilising KDT for (regional/rural 0/16, 0 %; metropolitan 49/98, 50 %; $p < 0.00001$) and all felt that lack of access to a KDT service was a barrier to epilepsy patient care (regional/rural 16/16, 100 %; metropolitan 67/98, 69 %; $p < 0.00001$).

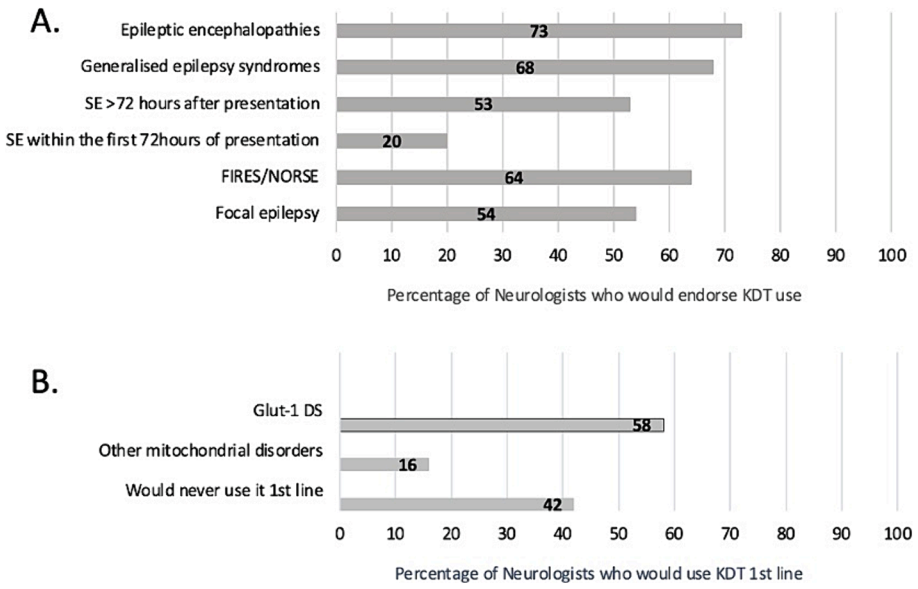

Fig. 1. Perceptions of appropriate indications for KDT use among neurologists (n = 114). A: Drug resistant epilepsies. and B: First line use in neurological disorders. Abbreviations: FIRES – Febrile Infection-Related Epilepsy Syndrome, NORSE – New Onset Refractory Status Epilepticus, GLUT-1 DS – Glucose Transporter Type 1 Deficiency Syndrome, SE – Status Epilepticus.

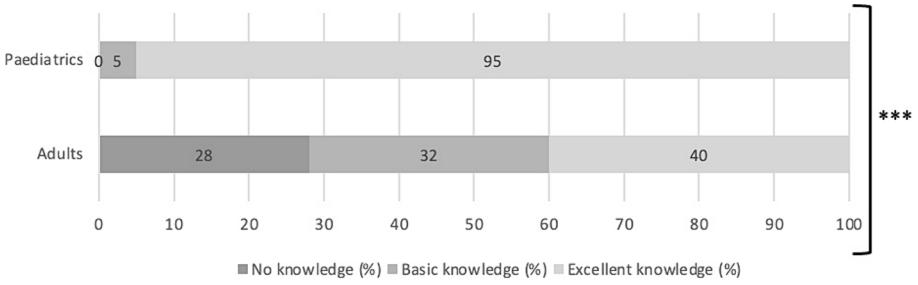

Fig. 2. Adult and paediatric neurologist awareness of KDT referral process. *** $p < 0.00001$.

Table 3
Sub analysis of significant paediatric and adult Neurologists responses.

	Total *N=114*	Adults N=*95*	Paediatrics *N=19*	P value
I have good/excellent knowledge of KDT for DRE	57	38 (40 %)	19 (100 %)	<0.00001
I have a strong knowledge of KDT for DRE and use it in my practice	27	12 (13 %)	15 (79 %)	<0.00001
I refer to my local KDT service	49	30 (32 %)	19 (100 %)	<0.00001
I understand current referral pathways	57	38 (40 %)	19 (100 %)	<0.00001
I am happy with current referral pathways	42	28 (29 %)	14 (93 %)	<0.00001
Better evidence is needed to increase my KDT referrals	63	62 (65 %)	1 (95 %)	<0.00001
There is a role for KDT use in SE	78	59 (62 %)	19 (100 %)	<0.00001
A clear referral pathway would increase my KDT referrals	73	67 (71 %)	5 (26 %)	<0.05
A clear KDT guideline would increase my KDT referrals	73	67 (71 %)	5 (26 %)	<0.05

4. Discussion

KDTs are an important part of providing care for young people and adults with drug resistant epilepsy, with increasing evidence and use internationally [18,19]. To improve delivery of KDT it is important to understand neurologists' current practices and factors influencing use of KDT and identify possible interventions that support quality, evidence-based, appropriate and equitable care. In this study of ANZ neurologists, there is marked variation in clinical practice and low use of KDT, with differences evident between paediatric and adult services, subspecialty and general neurology practices along with urban and rural/remote regions. Despite low current use and capacity to provide KDTs, ANZ neurologists endorse KDTs as an acceptable treatment for drug resistant epilepsy, indicating a substantial unmet need.

Contributing factors for poor KDT utilisation are seen in all three areas analysed by the COM-B model (Fig. 3). Low perceived knowledge regarding patient selection, diet initiation and management, difficulties in access to KDT services and concerns about the cost of KDT therapy were all identified as barriers affecting clinicians' capability and opportunity to prescribe KDT therapy. Clinicians' motivation to refer people with epilepsy for KDT was affected by perceived negative impacts for their patients, including social, domestic, financial and general health impacts, as well as compliance challenges. Taken together these findings inform our recommendations to increase knowledge of KDT in epilepsy among stakeholders and deliver resources that promote equitable models of integrated care. This could be achieved via a multimodal

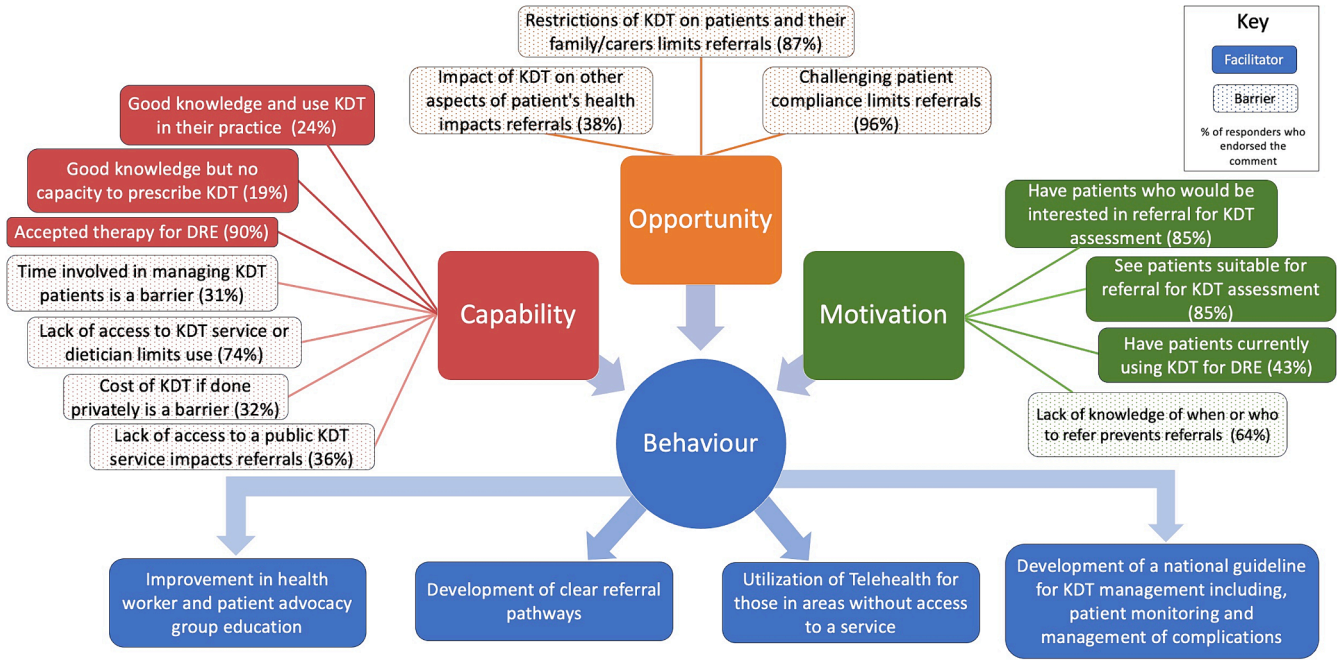

Fig. 3. Neurologists' behaviours and practices that influence use of KDT mapped to the Capability, Opportunity, Motivation and Behaviour (COM-B) Model[i] and recommendations to strengthen best practice.

approach including online modules, webinar clinical update meetings and educational sessions at the national neurology and intensive care society annual meetings.

Similar to international practice, in ANZ KDT is utilised as an advanced therapy in drug resistant epilepsy [20,21], however use in status epilepticus was lower. Of relevance, 5 recent cohort studies of between 2 and 15 patients, have reported tolerability along with resolution of super refractory status epilepticus in up to 80 %, including those experiencing months of unresolved SE [22,18,23]. In line with these findings, an international survey [24] reported use of KDT among 80 % of physicians for this and early implementation of KDT in people presenting with new onset refractory status epilepticus has been recommended by the International League Against Epilepsy [25]. Further education of local neurologists and intensivists is needed in the ANZ region to encourage earlier implementation and increased utilisation of KDT in this patient cohort.

Comparable to our findings, in 2021 access to dieticians and neurologists with KDT experience was recognised as challenge in several regions internationally [26]. As hypothesised, our study also found distinct differences accessing KDT services between metropolitan and regional/rural areas. In the broader literature, general health inequalities in regional/rural areas are similar and was the subject of a World Health Organisation integrative review in 2021, which highlighted the challenges faced in these communities due to workforce shortages as well as access and deficits in financial backing [27]. In addition, transport availability and distances to services were identified as significant barriers for regional/rural people [28].

Rapid adaptation of Telehealth services as a temporary measure during COVID-19 pandemic is now accepted as a permanent form of healthcare with potential to bridge heatlh inequity in ANZ [29]. Telehealth services have been successfully used internationally to implement KDT for epilepsy in patients as young as 3 years old, prior to and, during the COVID-19 pandemic utilising live and pre-recorded information sessions as well as phone, video, and email support [30,31,32]. Pre-existing Telehealth models [33], such as those used by the Telestroke service [34], could be utilised by patients in regional/rural ANZ or for patients from states/territories where KDT services are not available to enable more equitable access to the valuable therapy.

The perceived barriers among health professionals to KDT are similar to reports in other countries, including dietary restrictions, compliance, cost and impact on general health [9,35]. Countering these concerns, there is increasing evidence to support the safety of KDT in adults with epilepsy, including reduced cardiometabolic risk at 6 months [36,37]. In addition to reduced seizure burden or seizure freedom, broader person-centred benefits include improvements in behavioural problems, sleep problems and quality of life [38,39], relevant to shared decision making [39]. The ability to utilise less restrictive KDT variants, in particular MAD and LGIT, may reduce the risk of side effects while still having positive impact on seizure control [40,41].

4.1. Study strengths and limitations

To our knowledge, this first study examining perceptions of knowledge, use and experiences of KDT for epilepsy treatment in ANZ, using the Capability, Opportunity, Motivation and Behaviour (COM-B) model [1] a theory-based implementation framework. Despite these strengths, several study limitations warrant discussion. The survey was specific to the Australian and New Zealand health systems and a minority practice in rural/remote regions participated, possibly limiting the generalisability of our findings. Considering the 18 % response rate to the survey, these findings may also contain a degree of selection bias, with slightly higher representation from epileptologists and the more populous states of NSW and Victoria. Even so, with marked variation in clinical practice and low use of KDT, our findings are likely to be relevant nationally. Likewise, the reported barriers from neurologists in regional/remote regions in our study are similar to the issues generally described, namely limited access to medical treatment [42,43]. Furthermore, our study focussed on neurologists and their perspectives may not reflect those of the multidisciplinary team involved in provision of KDT, including nursing, allied health, people living with epilepsy and advocacy organisations.

4.2. Implications for clinical practice

Our research carries significant implications for future practice and highlights the unmet need for provision of KDT, facilitated by education,

clarity in pathways, and development of best practice guidelines. Important next steps include multi-stakeholder engagement and partnerships across the broader community (neurologists, nursing, allied health, researchers, patient advocacy groups and policy makers) to co-develop, design, and distribute resources for the use of KDT. Alongside telehealth, this is anticipated to facilitate greater accessibility, including for patients of different cultural, linguistic and education backgrounds. Improved education and awareness can also be achieved with addition to undergraduate and postgraduate medical curricula and continuing medical education programmes.

Building on our study findings, future research to increase knowledge of KDT efficacy, tolerability and patient centred outcomes and experiences in adolescents and adults are essential. Future implementation strategies should also include development of a contemporary and relevant best practice guidelines for KDT use in adolescents and adults with epilepsy as endorsed by neurologists in our study and an international clinician survey [36].

Ethics approval

The study was approved by the Sydney Children's Hospital Network Human Research Ethics Committee (Ethics Approval Number 2022/PID006898-2022/ETH00623).

This work is not under consideration for publication elsewhere and has not been previously published. If accepted the article will not be published elsewhere.

No Generative AI or AI-assisted tools were used in the formation of this paper.

The publication of this article is approved by all authors.

CRediT authorship contribution statement

Tania E. Farrar: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Arlene D'Silva:** Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation. **Michael Cardamone:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Melissa L. Bartley:** Writing – review & editing, Conceptualization. **Chong H. Wong:** Supervision, Writing – review & editing. **Michelle A. Farrar:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebr.2024.100711.

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