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Outcome measurement and reporting in childhood epilepsy treated with ketogenic diet therapy: a scoping review protocol

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Review question: The objective of this scoping review is to investigate the outcomes measured and reported in trials of children with refractory epilepsy treated with ketogenic diet therapy. The scoping review will aim to list the outcomes and map the associated components including intervention (type of ketogenic diet therapy), definition (if used) of the outcome, the tool or indicators used to measure the outcome, validity of tool used, the time from intervention commencement to measurement of the outcome and the reporting of the outcome. Specifically, the review question is: Which outcomes are measured and reported in studies of childhood epilepsy treated with ketogenic diet therapy?

Keywords Childhood; core outcome set; epilepsy; ketogenic diet; outcomes


Introduction

Epilepsy is a condition where individuals are prone to recurrent epileptic seizures. This may result from a number of different causes, although initial treatment remains antiepileptic medications. Although two-thirds of people will respond or enter spontaneous remission, up to one-third of children with epilepsy will be refractory to standard antiepileptic medication.¹ The International League Against Epilepsy (ILAE) describe refractory epilepsy as failure to achieve sustained seizure freedom with two appropriate and tolerated anti-epileptic drugs.² When resective epilepsy surgery is not feasible, other non-pharmacological treatments including ketogenic diet (KD) therapy are considered.³ The KD is a high-fat, restricted-carbohydrate regimen that has been used as a treatment for refractory epilepsy since its first reported use in 1921.⁴ There are many types of KD in use with varying degrees of dietary restriction. The classical KD is based on a ratio of fat to carbohydrate, usually 3:1 or 4:1.⁵ Long-chain triglycerides are the predominant fat source, carbohydrate is heavily restricted and protein is limited to that required for growth. The medium chain triglyceride (MCT) KD⁶ allows a slightly higher carbohydrate and protein intake than classical KD, as medium-chain triglyceride fat is absorbed and transported more efficiently than long-chain triglyceride fat, with greater ketone production per unit of dietary energy.⁷ In addition to the traditional KD, modified versions are often used and include the modified Atkins diet,⁸ modified KD used in the United Kingdom with similar principles to modified Atkins diet and the low glycemic index treatment.⁹ These modified versions take a less restrictive approach than the more traditional classical and MCT KDs, but the principles of high-fat and low-carbohydrate intake remain and require significant dietary adjustment for the child.

Ketogenic diet therapy is a well-established treatment for refractory epilepsy, with more than 50% of children achieving greater than 50% seizure reduction in retrospective and prospective observational studies.¹⁰-¹³ Three key randomized controlled trials (RCTs) assessing the efficacy of KD have been published: Neal et al.⁷ using the classical and MCT KD, Sharma et al.¹⁴ using the modified Atkins diet and Lambrechts et al.¹⁵ the MCT KD. In all three studies,
significantly more children treated with KD therapy experienced seizure reduction of at least 50% than those in the usual care control group; (38% versus 6%),5 (52% versus 11.5%)14 and (50% versus 18%).15 Neal et al.5 demonstrated that the classical and MCT KD were comparable in efficacy and tolerability.

Typically, seizure reduction or seizure freedom are the primary outcomes of choice with attrition, tolerability and adverse effects often considered secondary outcomes. A more holistic approach might also consider health-related quality-of-life outcomes, such as reduced hospitalization,16 reduced medication load and cost,17 and improved behavior and cognition.18 A recent Cochrane review19 found only one RCT assessing the effect of KD on quality of life, cognition and behavior. They suggest future studies should use validated tools to assess these outcomes. Standardized and validated tools such as the PedsQL,20 Child Health Questionnaire (CHQ)21 and the epilepsy specific Quality of Life in Childhood Epilepsy (QOLCE)22 questionnaire aim to assess the impact of chronic disease on childhood quality of life. However, shortcomings and challenges exist when applying these tools to populations with disability. In clinical practice, ketogenic teams try to address these shortcomings by developing alternative questionnaires tailored for parents or caregivers of children with chronic epilepsy.23

There is no general consensus on which outcomes should be reported in clinical trials for most clinical areas, including childhood epilepsy treated with KD therapy. Reaching consensus on a core set of outcomes would reduce outcome reporting bias, improve quality and relevance of research, improve reporting consistency and support meta-analysis leading to better informed healthcare decisions.24 The authors have chosen to conduct a scoping review to provide a descriptive overview of the outcomes currently measured and reported in childhood epilepsy. Prior to developing the present review protocol, preliminary searches were undertaken to identify any existing scoping or systematic reviews published or underway on a similar or identical topic. The JBI Database of Systematic Reviews and Implementation Reports, PROSPERO, Cochrane Database of Systematic Reviews, CINAHL and PubMed were searched and no relevant reviews were identified. This proposed scoping review will follow the approach recommended by the Joanna Briggs Institute (JBI).25,26 The scoping review methodology was chosen for its suitability for addressing the proposed aim—namely, to identify a comprehensive list of outcomes measured and reported in childhood epilepsy treated with KD therapy. Furthermore, this review will explore the definitions of outcomes, the tools or methods employed to measure the outcome, the time from KD therapy commencement to measurement of the outcome and the reporting of the outcomes. Collating and mapping this information will inform the process of developing a core outcome set for use in clinical practice and future research trials, using methodology recommended by the Core Outcome Measures in Effective Trials (COMET) Initiative.24

### Inclusion criteria

**Participants**
The scoping review will consider studies that include male and female children 18 years or younger with epilepsy treated with KD therapy for at least one month. Studies undertaken with adults will be excluded. Children treated with KD therapy for a diagnosis other than childhood epilepsy will be excluded (e.g. neuro-oncology and metabolic disorders).

**Concept**
The scoping review will consider studies that include male and female children 18 years or younger with epilepsy treated with KD therapy for at least one month. Studies undertaken with adults will be excluded. Children treated with KD therapy for a diagnosis other than childhood epilepsy will be excluded (e.g. neuro-oncology and metabolic disorders)

**Context**
The context of this review will be settings with pediatric patients undertaking KD therapy for refractory epilepsy.

**Types of studies**
This scoping review will consider both experimental and quasi-experimental study designs including RCTs, non-randomized controlled trials, before
and after studies and interrupted time-series studies. There are only seven RCTs examin-
ing KD therapy, so analytical observational studies including prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies will be considered for inclusion. The first RCT assessing the effectiveness of KD for childhood epilepsy\(^5\) and the first internationally agreed guidelines on the management of children treated with KD therapy were published in 2008.\(^3\) These two key publications have guided subsequent research and the clinical management of children treated with KD. Therefore, studies published from 2008 onwards will be included. Inclusion of a variety of study designs will ensure a large number of relevant studies will be reviewed, and repetition of measured and reported outcomes is expected. Studies published in English will be included. Systematic reviews will be excluded at the title and abstract screening phase. However, the reference lists will be reviewed to ensure all primary studies have been identified in the searches. The reference list of all studies selected for inclusion will be screened for additional studies.

**Methods**

The proposed systematic review will be conducted in accordance with the Joanna Briggs Institute methodology for scoping reviews.\(^25\)

**Search strategy**

The search strategy will aim to find both published and unpublished studies. An initial limited search of PubMed and CINAHL was undertaken, followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe articles. This informed the development of a search strategy tailored for each information source. A full search strategy for PubMed is detailed in Appendix I.

**Information sources**

The databases to be searched will include Cochrane Database of Systematic Reviews, Cochrane CENTRAL, CINAHL, PubMed, Scopus, Embase, AMED and JBI Database of Systematic Reviews and Implementation Reports. The trial registers to be searched will include ISRCTN registry and ClinicalTrials.gov. The search for unpublished studies will include the British Library e-theses online services (ETHOS) database, OAIster and OpenGrey (System for Information on Grey Literature in Europe; SIGLE). An expert in the field will be consulted to ensure no studies are missed.

**Study selection**

Following the search, all identified citations will be collated and uploaded into EndNote V8 (Clarivate Analytics, PA, USA) and duplicates removed. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. The reference list of systematic reviews will be reviewed to ensure all primary studies have been identified in the searches. The reference list of all studies selected for inclusion will be screened for additional studies.

Studies that meet the inclusion criteria will be retrieved in full and their details imported into the JBI System for the Unified Management, Assessment and Review of Information (SUMARI; Joanna Briggs Institute, Adelaide, Australia). Authors will be contacted to request full text access where necessary. Study protocols will be requested from authors of included studies to compare outcomes of interest. Full text studies that do not meet the inclusion criteria will be excluded, and reasons for exclusion will be provided in an appendix in the final scoping review report. The results of the search will be reported in full in the final report and presented in a PRISMA flow diagram.\(^27\)

**Data extraction**

Data will be extracted from papers included in the review by two independent reviewers (JC and KMM) using the standardized data extraction tool available in JBI SUMARI. As a minimum, the following data will be extracted: study type, author details, journal of publication and year, participant characteristics, intervention (type of KDTherapy), each outcome reported, definition (if used) of outcome, the tool or indicators used to measure the outcome, validity of tool used, the time from intervention commencement to measurement of the outcome and the reporting of the outcome. A draft data extraction tool is provided (Appendix II). This will be modified and revised as necessary during the process of extracting data from each included study. Modifications will be detailed in the full scoping review report. Any disagreements that arise between the reviewers (JC and KMM) will be resolved through discussion or with a third reviewer (HC). Authors of papers will be contacted to request missing or additional data where required.
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Data presentation
The extracted data will be presented in a diagrammatic or tabular form in a manner that is most relevant to the objective and questions of this scoping review. The tables and charts will report on the outcomes measured and reported by researchers, the definitions used to describe these outcomes and the method of measurement. A narrative summary will accompany the tabulated and/or charted results and will describe how the results relate to the reviews objective and questions. This scoping review is phase one of a larger project in which the overall aim is to develop a core outcome set for refractory childhood epilepsy treated with KD therapy. The study will identify the outcomes to be measured in clinical effectiveness trials but will also guide audit or service evaluation in clinical practice. Parents, health care professionals, researchers and relevant charities will be consulted to ensure the final core outcome set reflects the interests of all and facilitates future decision making. The study is registered as 1116 on the COMET database of core outcome set studies (http://www.comet-initiative.org/studies/details/1116).

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References
20. Varni JW, Limbers CA. The Pediatric Quality of Life Inventory: measuring pediatric health-related quality of life from the...
Appendix I: Search strategy for PubMed


AND

Epilepsy [MeSH] OR seizure*[tiab] OR epilep*[tiab]

AND


Limits: 10 years. Search returned 461 records.
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Appendix II: Data extraction form

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Country</th>
<th>Year</th>
<th>Study design</th>
<th># of subjects</th>
<th>Attrition</th>
<th>Duration</th>
<th>Age range</th>
<th>Primary epilepsy-related diagnosis</th>
<th>Type of ketogenic diet</th>
<th>Outcome</th>
<th>Definition of outcome</th>
<th>Is this stated to be the primary outcome?</th>
<th>Is this stated to be a secondary outcome?</th>
<th>Outcome not stated a priori</th>
<th>Responder (parent or clinician)</th>
<th>Measurement tool</th>
<th>Validity of measurement tool</th>
<th>Time points at which outcome measured</th>
<th>Protocol obtained?</th>
<th>Outcome reported in results?</th>
<th>Outcomes stated in protocol reported in paper?</th>
<th>General comments</th>
</tr>
</thead>
</table>