ONTARIO EPILEPSY GUIDELINES

Version 2.0, Updated January 2023

Provincial Guidelines for the Management of Drug-Resistant Epilepsy in Adults and Children who are not Candidates for Epilepsy Surgery

EPLINK

THE EPILEPSY RESEARCH PROGRAM OF THE ONTARIO BRAIN INSTITUTE

ONTARIO BRAIN INSTITUTE INSTITUT ONTARIEN DU CERVEAU

These Guidelines are a Product of Critical Care Services Ontario (CCSO) and EpLink – The Epilepsy Research Program of the Ontario Brain Institute

The Provincial Guidelines for the Management of Drug-Resistant Epilepsy in Adults and Children who are not Candidates for Epilepsy Surgery is the result of a collaborative effort between CCSO, the Epilepsy Implementation Task Force (EITF), and Provincial Neurosurgery Ontario (PNO). The EITF was established in June 2013 to develop and implement a provincial framework to maximize value from the system of epilepsy care in Ontario. To support the flow of patients towards appropriate treatment for epilepsy, this document contains a set of guidelines to help with the diagnosis, treatment and referral practices from the moment of a patient's first seizure. CCSO supports the work of the EITF, a subgroup of PNO, as part of its mandate to support equitable and timely access to neurosurgical care, including epilepsy surgery, and to help maintain the province's neurosurgical capacity.

These guidelines are maintained and updated by EpLink – The Epilepsy Research Program of the Ontario Brain Institute (OBI) in partnership with the EITF.

How to Use This Document

The Guidelines included in this document have been developed by a sub-group of the Epilepsy Implementation Task Force for any health care provider engaged in the care of patients with epilepsy before referral to surgery. The guidelines are based on current processes and represent expectations for the highest standards of epilepsy care.

This document provides recommendations only.

Disclaimer: *The contents of these Guidelines may change over time. Clinicians and hospital administrators should use sound judgment for individual patient encounters. EpLink, Critical Care Services Ontario, the Epilepsy Implementation Task Force and Provincial Neurosurgery Ontario strongly recommend evidence-based practices.*

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Please see Appendix 11 for a list of the original EITF membership.

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LIST OF ABBREVIATIONS

ASM	Anti-seizure Medication (also known as antiepileptic or anticonvulsant drug)
CPSO	College of Physicians and Surgeons of Ontario
CPO	College of Psychologists of Ontario
CSF	Cerebrospinal Fluid
CT	Computerized Tomography
DBS	Deep Brain Stimulation
DRE	Drug-Resistant Epilepsy
DS	Dravet Syndrome
ECG	Electrocardiography
ED	Emergency Department
EEG	Electroencephalography
EMU	Epilepsy Monitoring Unit
EITF	Epilepsy Implementation Task Force
eTNS	External Trigeminal Nerve Stimulation
FHP	First Healthcare Provider
FP	Family Physician
GP	General Practitioner
ILAE	International League Against Epilepsy
LGS	Lennox-Gastaut Syndrome
LGIT	Low Glycemic Index Therapy
LP	Lumbar Puncture
KD	Ketogenic Diet
MAD	Modified Atkins Diet
MRI	Magnetic Resonance Imaging
NES	Non-epileptic seizures
NP	Nurse Practitioner
OCSWSSW	Ontario College of Social Workers and Social Service Workers
PNO	Provincial Neurosurgery Ontario
RCT	Randomized control trial
RD	Registered Dietitian
RE	Rasmussen's Encephalitis
SUDEP	Sudden Unexpected Death in Epilepsy
TDM	Therapeutic Drug Monitoring
TMS	Transcranial Magnetic Stimulation
TSC	Tuberous sclerosis complex
WWE	Women with Epilepsy
VNS	Vagus Nerve Stimulation

DEFINITIONS

Adolescent	A person 13 to 17 years of age.
Adolescent Medicine Specialist	Pediatrician practising adolescent medicine.
Child	A person less than 18 years of age.
Child Life Specialist	Baccalaureate degree certification as Certified Child Life Specialist (CCLS) issued by the Child Life Council (CLC).
Community Epilepsy Agencies	Agencies that provide a range of support services to persons with epilepsy and their families. These services include epilepsy information, seizure first aid training, support groups, social opportunities, employment counseling and school advocacy.
Co-morbidity	Co-morbidity refers to the co-occurrence of two conditions with a greater frequency than found in the general population. This does not infer a causal relationship. Co-morbid conditions are common in people with epilepsy. They are found across the lifespan and have important implications for treatment and quality of life.
Drug-Resistant Epilepsy	(Also known as medically refractory or pharmacoresistant epilepsy) Failure of adequate trials of two tolerated, appropriately chosen and used anti-seizure medications (whether as monotherapy or in combination) to achieve sustained seizure freedom (Kwan, 2010 from International League Against Epilepsy).
Epileptologist	Qualifications and Training: 1) Clinical fellowship training in epilepsy and video-EEG for at least 12 months in a specialized center in Canada, US or abroad; 2) Recognized as a neurologist by the College of Physicians and Surgeons of Ontario (CPSO); and 3) Certification for EEG reporting (EEG examination by the Canadian Society of Clinical Neurophysiologists or APBN exam in Epilepsy) is mandatory. Neurologists who have/had been reporting Video EEG recordings without supervision in any jurisdiction in Canada or the United States of America anytime in or before 2013 are exempt from EEG/Epilepsy examination.
Epileptic Seizure	A transient occurrence of signs and/or symptoms due to abnormal excessive and/or synchronous neuronal activity in the brain (Fisher et al, 2005).
Epilepsy	Epilepsy is a disease of the brain defined by any of the following conditions: 1) At least two unprovoked (or reflex) seizures occurring >24 h apart 2) One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years 3) Diagnosis of an epilepsy syndrome (Fisher et al, 2014)

DEFINITIONS continued

Epilepsy Surgeon	Qualifications and Training: 1) Clinical fellowship training in Epilepsy Surgery in specialized center in Canada, US or abroad 2) Recognized as a neurosurgeon by the College of Physicians and Surgeons of Ontario (CPSO)
Family Physician	A physician recognized by the CPSO as a family physician.
General Practitioner	A physician licensed by the CPSO for general practice.
Internist	A physician recognized by the CPSO as a specialist in Internal Medicine.
Neurologist	A physician recognized by the CPSO as a specialist in Neurology.
Neuropsychologist	A psychologist registered with the College of Psychologists of Ontario (CPO) for the practice of clinical neuropsychology.
Nurse Practitioner	A nurse registered with the College of Nurses of Ontario in the Extended Class.
Pediatrician	A physician recognized by the CPSO as a specialist in Pediatrics.
Psychiatrist	A physician recognized by the CPSO as a specialist in Psychiatry.
Psychologist	A healthcare provider registered with the College of Psychologists of Ontario (CPO) for the practice of clinical psychology.
Registered Dietitian	A dietitian registered with the College of Dietitians of Ontario. RDs without previous experience in diet therapies for epilepsy should receive training from a registered dietitian who practices diet therapies for epilepsy.
Social Worker	A healthcare provider registered as a social worker with the Ontario College of Social Workers and Social Service Workers (OCSWSSW).
Senior	A person 65 years of age or older.
Specialists	Internists, pediatricians, and neurologists.

1. Introduction

Epilepsy affects around 134,000 Ontarians, of whom approximately 117,000 are adults and 17,000 are children under the age of 18 (Ontario Brain Institute, 2023). An estimated 30% of those diagnosed will experience seizures that do not respond to treatment with two or more appropriate anti-seizure medications (ASMs) and are considered to have drug-resistant epilepsy (Kwan & Brodie, 2000). These numbers are not static. Each year it is estimated that 9,000 Ontarians will develop epilepsy, and 2,700 of them will have drug-resistant epilepsy (Tellez-Zenteno et al. 2004; Wiebe et al. 1999, Ontario Brain Institute, 2023).

In some patients with drug-resistant epilepsy, surgical intervention could be successful in eliminating seizures; there is approximately a 55-66% chance that an individual with temporal lobe epilepsy will be seizure-free after surgery (McIntosh et al., 2004; Tellez-Zenteno et al., 2005), resulting in significantly better outcomes with respect to seizure freedom, improved quality of life, and reduction of psychosocial comorbidities that accompany drug-resistant epilepsy than continued medical treatment (Bowen et al. 2012). However, not all individuals with epilepsy are candidates for surgery – approximately one third of those suffering from medically-refractory epilepsy will not be considered candidates (Bowen et al. 2012).

Despite its effectiveness, surgical treatment is underutilized in Ontario, with only a fraction of the population who may be eligible for surgery assessed every year. A 2012 report by the Expert Panel on a Provincial Strategy for Epilepsy Care (Health Quality Ontario [HQO], 2012) identified that long wait lists at the province's Epilepsy Monitoring Units (EMUs) and low referral rates contributed to the underutilization of surgical treatment. The Panel also noted that awareness of surgical treatment options was poor and patients were not diagnosed, treated and referred appropriately. A 2011 estimate determined that less than 2% of potential surgical candidates accessed surgical treatment (HQO, 2011).

The Panel recommended action to improve epilepsy care infrastructure and surgical referral in the Province (HQO, 2012). As a result, the Ministry of Health and Long-Term Care (MOHLTC) made an investment of 21 new Epilepsy Monitoring Unit (EMU) beds in Ontario, bringing the total number of EMU beds to 43 (29 adult and 14 paediatric). The Ministry also resourced additional epilepsy surgery and neuromodulation capacity through Critical Care Services Ontario's (CCSO) Provincial Neurosurgery Strategy and established the Epilepsy Implementation Task Force (EITF) to oversee epilepsy system improvements.

1.1. Epilepsy Implementation Task Force

The Epilepsy Implementation Task Force (EITF) was formed in June 2013 to develop and implement a provincial approach to an integrated system for epilepsy care in Ontario. Supported by CCSO, this committee was co-chaired by Dr. Carter Snead, Pediatric Neurologist at the Hospital for Sick Children, and Brenda Flaherty, Executive VP and Chief Operating Officer at Hamilton Health Sciences.

The EITF brought together senior clinical and administrative leaders from the epilepsy community to:

- Improve access along the full continuum of care by coordinating resources and wait lists;
- Establish standardized diagnostic and surgical protocols across hospitals with comprehensive epilepsy programs; and
- Develop supports for primary care providers.

The EITF was a subgroup of Provincial Neurosurgery Ontario (PNO), a committee working to develop a comprehensive provincial neurosurgical system. The EITF worked in collaboration with PNO to support equitable and timely access to neurosurgical care, including epilepsy surgery, and to help maintain the province's neurosurgical capacity. This work was supported by the Ministry through CCSO (www.criticalcareontario.ca). For a list of EITF membership, please see Appendix 11.

The creation of the EITF stemmed from the expert panel report to Health Quality Ontario assessing the challenges to access in epilepsy care in Ontario (HQO, 2012). The report notes that the community of healthcare providers treating epilepsy needs support with a standardized approach to diagnosis and treatment (such as ASMs, electroencephalography (EEG) or neuroimaging), and process for referral to a neurologist or for surgery (if the seizures are determined to be medically refractory). This document is the outcome of the recommendation to provide province-wide guidelines for first-contact healthcare providers (such as primary care and emergency department physicians) to standardize the diagnosis, treatment and referrals of patients with epilepsy in the province.

1.2 Epilepsy care in Ontario

In order to maximize value and ensure that patients are receiving timely, high quality care, it is crucial to clarify system capacity and referral paths. This will help set clear expectations for planning, coordination and performance for all hospitals with specialty epilepsy care programs.

The EITF has developed a definition of a Comprehensive Epilepsy Program (CEP) and established a planning and integration framework for epilepsy care in Ontario:

A CEP is an integrated care model for the management of individuals with epilepsy within a multidisciplinary team. A CEP covers various aspects of care including medical, psychosocial, and nutritional management, appropriate neurodiagnostic investigations, a mandatory EMU, capability for presurgical diagnostic evaluation, and established links to Community Epilepsy Agencies.

Hospitals with CEPs are divided into two categories based on the level of services they provide:

1. A District Epilepsy Centre (DEC) houses a comprehensive epilepsy program that provides all appropriate epilepsy related clinical services but not all types of epilepsy surgery. A DEC should provide basic investigations necessary to determine candidacy for epilepsy surgery including assessment by an Epileptologist, and full EMU service including neuropsychological evaluations.

Some DECs may also perform surgical procedures such as vagal nerve stimulator implantation and temporal lobectomies.

The following hospitals are classified as District Epilepsy Centres:

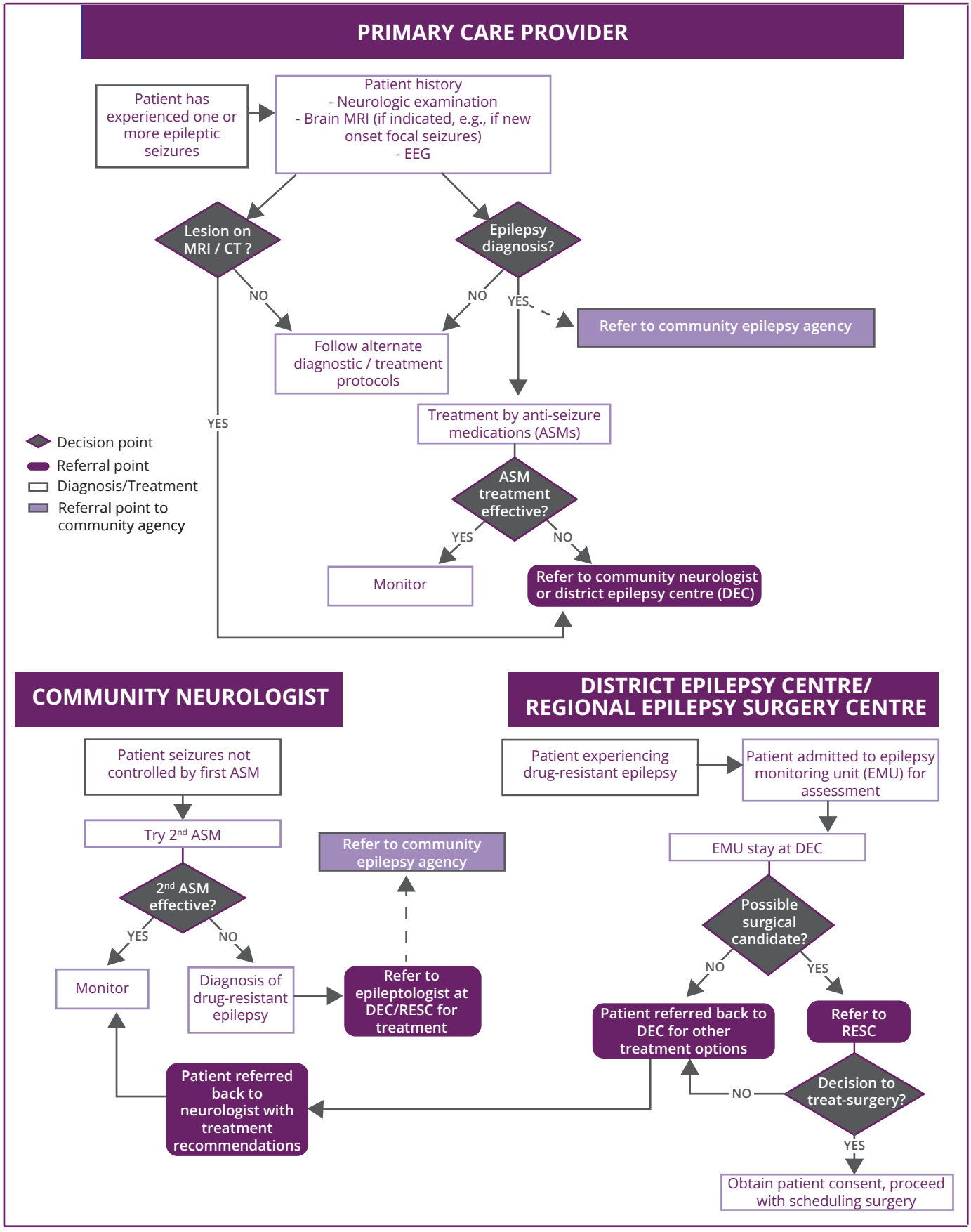
Hospital	Adult beds	Paediatric beds
Hamilton Health Sciences (HHS)	3	2
Kingston General Hospital (KGH)	3	1
The Ottawa Hospital (TOH)	2	-
Children's Hospital of Eastern Ontario (CHEO)	-	2

2. A Regional Epilepsy Surgery Centre of Excellence (RESC) is a facility with a comprehensive epilepsy program that provides all the services available in a DEC, and in addition, epilepsy surgery including facility for intracranial monitoring. An RESC is also a DEC for its catchment area.

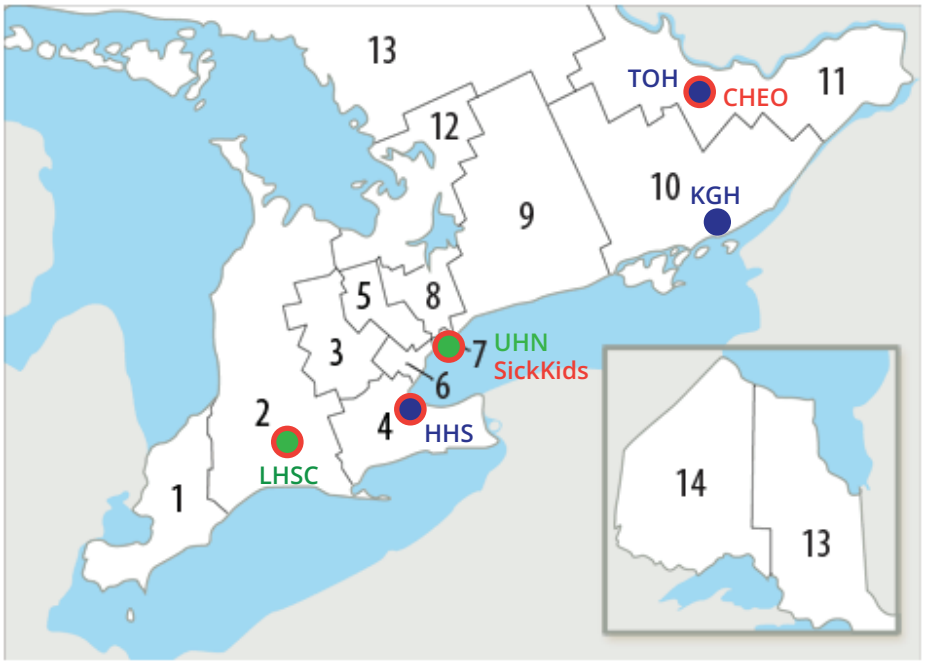
The following hospitals are classified as Regional Epilepsy Surgery Centres of Excellence:

Hospital	Adult beds	Paediatric beds
London Health Sciences Centre (LHSC)	11	2
Hospital for Sick Children (SickKids)	-	7
University Health Network (Toronto Western Hospital) (UHN)	10	-

Patient Referral Pathway



Map of Ontario's Epilepsy Centres by Home and Community Care Support Services regions



- District Epilespy Centre (DEC)
- Regional Epilepsy Surgical Centre (RESC)
- Pediatric Centre

1.3 About this document

The EITF developed the first edition of this document in an effort to provide guidelines for evidence-based practice for all healthcare providers in Ontario who provide primary point of care for patients with epilepsy. This second edition of the Guidelines has been prepared under the purview of EpLink, the epilepsy research program of the Ontario Brain Institute. Based at the University of Toronto, EpLink supports and manages research projects at hospitals and universities across Ontario and is focused on finding new ways to diagnose, treat and improve quality of life for people with epilepsy. As the mandate of the original EITF is now complete, the guidelines series will be updated and maintained by EpLink.

1.4 Target audience

The intended target audience of these guidelines is mainly Epileptologists but includes Neurologists, Family Physicians (FP), Nurse Practitioners (NP), Registered Dietitians, Paediatricians, Internists, Emergency Physicians and Community Epilepsy Agencies. The guidelines should be shared with anyone involved in the care of patients with epilepsy. It should be noted that these guidelines were developed in specific populations treated at tertiary care centres and may not fully reflect the diversity of the epilepsy population in Ontario or inequities in access to care.

1.5 The EITF guidelines series

The Epilepsy Implementation Task Force developed a series of guidelines intended to support primary care providers, community neurologists, and District and Regional Epilepsy Centres. These guidelines aim to increase the awareness of, and referrals to, appropriate diagnostic assessment and surgical care of patients in Ontario.

For Primary Care Providers:

1. Provincial Guidelines for the Management of Epilepsy in Adults and Children (January 2015; updated March 2020)

To support the flow of patients towards appropriate treatment for epilepsy, this document contains a set of guidelines to help with the diagnosis, treatment and referral practices from the moment of a patient's first seizure.

2. Provincial Guidelines for Epilepsy Surgery Referrals in Ontario (May 2015)

This document provides an approach to referral of drug-resistant epilepsy patients by defining evidence-based indications to epilepsy surgery in all age groups, with careful consideration given to age-specific issues ranging from infants to the elderly.

3. Provincial Guidelines for the Management of Drug-Resistant Epilepsy in Adults and Children Who are not candidates for Epilepsy Surgery (March 2016; updated January 2023)

This guideline provides an approach to the management of the patient with drug-resistant epilepsy in whom surgical treatment is not an option. It includes the use of anti-seizure medications, cannabis, and non-pharmacological therapies such as dietary management and neuromodulation.

4. Provincial Guidelines for Transitional Care of Paediatric Epilepsy Programs to Adult (Feb 2017; next review 2021)
To ensure uninterrupted quality medical care for adolescent patients with chronic disorders, this document provides guidelines for paediatric and adult practitioners to assist in the seamless transition of epilepsy care for adolescents who are departing the paediatric system and entering the adult health care network.

For Providers and Administrators in District and Regional Epilepsy Centres:

5. Provincial Epilepsy Monitoring Unit (EMU) Guidelines for Ontario (January 2014)
This document outlines protocols and provides guidelines for EMUs for diagnostic evaluation for epilepsy. It can be used as a guide for neurosurgical centres with EMU beds.

6. Provincial Guidelines for Regional Epilepsy Surgical Centres of Excellence (May 2016)
This document presents best practice guidelines and sets out accountabilities for hospitals and their collaborative interdisciplinary teams that provide care for patients at Regional Epilepsy Surgical Centres of Excellence.

2. Incidence and Demographics

In this document the term 'drug-resistant epilepsy' (DRE) refers to those epilepsies where there has been a failure of two anti-seizure drugs (ASMs).

The term 'drug resistant epilepsy' has been preferred to 'medically refractory epilepsy' by some authors and is used by the International League Against Epilepsy (ILAE); defined as failure of adequate trials of two tolerated and appropriately chosen and used ASMs (whether as monotherapies or in combination) to achieve sustained seizure freedom (Kwan et al. 2010). The term 'intractable epilepsy' has also been used as a synonym for medically refractory epilepsy. Determining the epidemiology of DRE is challenging, as the definition varies widely across studies, with only 12% meeting the requirements of the ILAE definition (Kalilani et al., 2018). In addition, drug response can be a dynamic process, with periods of seizure freedom and recurrence (Brodie et al., 2012).

There is little evidence-based data showing that the management of DRE effectiveness (seizure control and lack of side effects) of an ASM is more important than efficacy (seizure control alone). Side effects of ASMs are an important reason why treatment is changed. 37% of patients with epilepsy develop DRE (Kwan and Brodie 2000). Although 82% of patients with idiopathic/genetic generalized epilepsy achieve seizure freedom, only about 26% of those with symptomatic or cryptogenic epilepsy become seizure-free (Semah et al. 1998). In children, 55% of those with symptomatic generalized epilepsy are drug-resistant (Berg 2001).

A number of factors may be used to predict whether epilepsy will be drug-resistant including the type of epilepsy, younger age at onset, underlying syndrome, etiology, EEG abnormalities, seizure frequency, density and tendency to cluster, environmental factors and genetic factors affecting ASM pharmacodynamics (French 2007; Mohanraj and Brodie 2006; Janmohamed et al. 2020; Sultana et al., 2021). Among clinical variables, having a neurologic deficit, symptomatic epilepsy, EEG abnormalities and high baseline seizure frequency are the most commonly reported predictors for less pharmacoresponsive epilepsy.

The management of DRE includes:

1. Review of the diagnosis of episodic paroxysmal events that are not epilepsy:

- Non epileptic seizures (NES, also known as psychogenic non-epileptic seizures or functional seizures): 30% of patients with presumed 'drug-resistant epilepsy' may have NES (Mohanraj and Brodie 2006). Particular difficulty to differentiate and manage arises when a patient has both epilepsy and NES.
- Cardiogenic (arrhythmias) and vasovagal events (syncope)
- Parasomnias
- Movement disorders (paroxysmal dyskinesias, cataplexy)

2. Medication-related problems:

- Therapy non-compliance
- Enzyme induction, especially if more than one ASM or other medication is used
- Inadequate ASM therapy

3. Consideration of further investigations as outlined below:

- Carefully review clinical history (including family history, health history) and seizure semiology (current and past), lifestyle (recreational drug use, alcohol abuse, sleep-deprivation), seizure triggers, post-ictal state
- Review response to current ASMs and previous ASMs including doses to assess if appropriate/ adequate dosing
- Repeat EMU admission or video EEG monitoring to characterize seizures
- Lumbar puncture if infectious or autoimmune process suspected
- Repeat or obtain brain imaging with 3T MRI using an epilepsy protocol (if not previously performed) to rule out potential lesion (e.g. hamartoma, mesial temporal sclerosis, cortical dysplasia, low-grade glioma) or if no neuroimaging was done at the time of diagnosis
- Review previous investigations – screening metabolic studies, autoimmune epilepsy panel, genetic epilepsy panel

3. Management of Drug-Resistant Epilepsy (in patients who are not candidates for surgery)

This section is intended to follow from the discussion on the management of epilepsy detailed in *Provincial Guidelines for the Management of Epilepsy in Adults and Children*.

Key areas of focus in managing drug-resistant epilepsy patients who are not candidates for surgical interventions include anti-seizure medications, immunotherapy, diet, neuromodulation and non-pharmacological considerations. These are discussed in the following sections and may be considered for use in combination and under the care of a multidisciplinary care team.

3.1 Anti-seizure medication (ASM) therapy

Currently, there are around two dozen ASMs available in Ontario. Given that there are few robust randomized controlled trials or comparative studies, determining which ASM to use can be challenging (Glauser et al. 2006; Glauser et al. 2013). The following general principles can be applied. If the trial of two ASMs is found to be ineffective by a neurologist, patients should be referred to an epileptologist as per the Provincial Guidelines for the Management of Epilepsy in Adults and Children.

Practice recommendations for ASM trials:

1. Optimise the dose of each ASM by increasing the dose incrementally. If the maximum dose is ineffective, introduce a second ASM while continuing on the first. If seizure control is achieved, consider tapering the first ASM. The advice to "start low and go slow" is appropriate (French 2004).

2. If one or two ASMs are ineffective, rational polytherapy should be explored. This treatment approach combines ASMs with different mechanisms of action (see discussion on following page). However, although mechanisms of action have been described for a number of ASMs, it is not certain that these are their only mechanisms of action or even the most important. For example, Levetiracetam (LEV) affects the SV2A receptor on the synaptic vesicle but also has calcium channel modulating effects and GABAergic properties. There is little systematic study of rational polytherapy. Considerations include a higher incidence of side effects when multiple ASMs are used.

3. Avoid using an ASM that may worsen or provoke seizures. Carbamazepine (CBZ), Oxcarbazepine (OXC), Phenytoin (PHT), Vigabatrin (VGB) and Tiagabine (TGB) may worsen myoclonus and absence seizures. Gabapentin (GBP) and Lamotrigine (LTG) may worsen myoclonus (Ben-Menachem 2014). Benzodiazepines given intravenously may worsen tonic seizures but may be very useful in treating Lennox-Gastaut and does not contraindicate their use (Somerville 2009).

4. Select ASMs according to the profile of the patient (including comorbidities and other medications) and the expected side effects.

5. Other factors that may affect ASM selection include cost of the drug and prescription drug coverage.

Recent literature has concentrated on the most recently introduced ASMs. There have been few class 1 studies and no comparative studies done on these new ASMs (French 2004; Glauser 2013). The most recently available ASMs are rufinamide, lacosamide, perampanel, eslicarbazepine, brivaracetam, fenfluramine, and stiripentol.

A list of selected common and serious adverse effects is provided in Table 1.

Despite the agreed need for consideration of many factors in deciding which ASM to use, the most important consideration is still the type of epilepsy. Greater precision can be applied when a particular epilepsy syndrome is identified (e.g. childhood absence epilepsy, juvenile myoclonic epilepsy) but many patients do not have an easily identifiable syndrome. Using a broad-spectrum ASM may be an efficient approach for the large number of children who do not have a defined epilepsy syndrome.

Table 1: Selected side effects of anti-seizure drugs (adapted from Kanner & Bicchi, 2022)

Anti-seizure medication	Selected side effects
First generation	
Clobazam	Somnolence, sedation, dizziness, ataxia, irritability, depression
Clonazepam	Somnolence, sedation, mood and behavioural changes
Phenytoin	Gingival hyperplasia (60%) and hirsutism, osteopenia/ osteoporosis, cardiac arrhythmia (0.8%), SJS (1-10 per 10 000 new users)[a]
Ethosuximide	Vomiting, gastrointestinal upset, depression, irritability, psychotic symptoms, SJS[a]
Carbamazepine	Hyponatremia (1%-40%), neutropenia, osteopenia/ osteoporosis, SJS (1-10 per 10 000 new users)[a]
Valproic acid[b]	Thrombocytopenia/ neutropenia (1%-30%), weight gain (up to 70%), osteopenia/ osteoporosis, pancreatitis (1 in 3000 to 1 in 5000 cases), hair loss, tremor, liver dysfunction, hyperammonemia
Second generation	
Gabapentin	Weight gain (2%-3%), peripheral edema (2%-8%)
Lamotrigine[b]	Headaches (1%-5%), insomnia (5%-10%), tremor (4%-10%), rash (5%-17%), SJS (1-10 per 10 000 new users)[a] , QRS prolongation
Topiramate[b]	Weight loss (4%-17%), memory problems and word finding difficulties (1%-11%), nephrolithiasis (3%)
Levetiracetam	Psychiatric symptoms (7%-25%)
Oxcarbazepine	Hyponatremia (1%-46%), osteopenia/ osteoporosis, thrombocytopenia, SJS[a]
Zonisamide[b]	Psychiatric symptoms (1%-9%), memory problems and word finding difficulties (10%-15%), SJS, nephrolithiasis (4%)
Third generation	
Brivaracetam	Somnolence, dizziness, nervousness/agitation, vertigo, headache, nausea, fatigue
Fenfluramine	Decreased appetite, pyrexia, fatigue, diarrhea, lethargy and somnolence
Lacosamide	Dizziness (16%-30%), drowsiness (5%-17%), cardiac arrhythmia
Eslicarbazepine	Hyponatremia (1%-2%), SJS[a]
Perampanel	Somnolence, dizziness, depression, aggression
Stiripentol	Drowsiness, cognitive impairment, ataxia, diplopia, nausea, abdominal pain, loss of appetite

Abbreviations: ASM, antiseizure drug; CYP, cytochrome P450; GABA, γ-aminobutyric acid; GTC, generalized tonic-clonic; LDL, low-density lipoprotein; LFTs, liver function tests; PGP, P-glycoprotein; SJS, Stevens-Johnson syndrome; UGT, glucuronosyltransferase.

[a]HLA-B*1502 should be tested in any patient of Asian descent, particularly Han Chinese, to minimize the risk of severe rash.

[b]ASMs with >2 mechanisms of action.

These broad spectrum ASMs are:

- Valproate
- Levetiracetam (Doumbia-Ouattara et al. 2011)
- Lamotrigine
- Topiramate
- Clobazam (Canadian Study Group for Childhood Epilepsy 1998)
- Brivaracetam
- Perampanel

Options for ASM use are set out in the *Provincial Guidelines for the Management of Epilepsy in Adults and Children*.

Results of the SANAD II RCT suggest that for people with generalized epilepsies, valproate is more clinically effective and cost-effective than lamotrigine and levetiracetam. Although clinically indicated and very efficacious for generalized epilepsies, valproate use is associated with significant potential adverse effects that may result in the use of other medications as first line agents. In addition, the use of valproate in women of child-bearing age is not recommended due to the risk of major congenital malformations (see section 8 in *Provincial Guidelines for the Management of Epilepsy in Adults and Children*). Ethosuximide and valproate have similar efficacy for absence epilepsies but ethosuximide is not effective for other seizure types (i.e, generalized tonic-clonic seizures and myoclonic seizures) (Marson et al., 2021). For people with focal epilepsy, the SANAD II results suggest that although both levetiracetam and zonisamide have efficacy when used as monotherapy, the evidence does not support their use as first-line treatments. Lamotrigine is associated with fewer adverse reactions and superior 12-month remission rates and should remain the first-line treatment in those with newly diagnosed focal epilepsy. In addition to efficacy and effectiveness data, the age of patient, concomitant medications, potential side effects, ease of use and cost to the patient should also be considered.

Newer ASMs have a better side effect profile, better tolerability and pharmacokinetic profile. A list of the known actions of currently available ASMs is shown in Table 2 and several authors (Kwan and Brodie 2006; French and Fraught 2009; Brodie and Sills 2011; Brigo et al. 2013) have advocated using ASMs based on their mechanisms of action in refractory epilepsy cases. This approach is relatively new and a significant criticism is that knowledge of the mechanisms of action of individual ASMs is incomplete. Some ASMs are known to have multiple mechanisms (see Table 2). This approach has not been tested in any rigorous clinical trials given the potential for an enormous number of combinations (McCabe 2015).

General ASM mechanisms of action:

1. Blocking excitatory channels
   - Presynaptic voltage-gated Na^+ channel
   - Presynaptic vesicle membrane receptor (SV2A)
   - Postsynaptic AMPA receptor (antiglutamatergic)
   - Postsynaptic T-type Ca^{2+} channel

2. Enhancing inhibitory channels
   - Presynaptic Ca^{2+} channel
   - Presynaptic γ-aminobutyric acid (GABA) transporter type 1 (GAT1) channel
   - Postsynaptic $GABA_A$ receptor (Cl^-)

3. Other mechanisms (see Table 2)

Ideal ASM polytherapy would combine supra-additive (synergistic) efficacy with infra-additive toxicity. Table 2 is intended to encourage the use of ASMs with different mechanisms of action rather than combining ASMs with the same mechanism of action. Limited data has suggested the following combinations (Brigo 2013):

Lamotrigine-Valproate* (focal seizures)
Ethosuximide-Valproate (absence seizures)
Lacosamide-Levetiracetam (focal seizures)
Stiripentol-Clobazam (Dravet syndrome)

*N.B.: This combination has the best human evidence for synergy, especially for focal seizures. The question of whether the addition of valproate (VPA) causes apparent synergy by inhibiting lamotrigine metabolism and increasing lamotrigine levels has been studied and the limited data does not show this. Nonetheless, because of the recognized effect of VPA on lamotrigine, the latter drug should be introduced very cautiously in patients on VPA. Current practice would be to use doses of lamotrigine that are 50% of usual introductory doses and in children a maximum dose of 5 mg/kg/day is suggested. However, the introduction of VPA in someone who is already on lamotrigine is said not to cause any risk for sensitivity reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis.

Table 2: Proposed Pharmacological Targets for ASMs (Modified from Kwan & Brodie, 2006)

Drug	Sodium Channels	Calcium Channels/ Currents	GABA-mediated inhibition	Glutamate Receptors	Presynaptic release machinery	Other
Benzodiazepines			+++			Abuse potential may limit use
Brivaracetam					+++ (SV2A receptor)	
Carbamazepine	+++	+	+			Modulates brain adenosine
Phenobarbital			+++			Abuse potential may limit use in adults. Although used frequently in neonates and infants, side effect profile may limit use in children.
Primidone			+++			Abuse potential may limit use
Eslicarbazepine acetate	+++					
Ethosuximide		+++ (Modulates T-type currents)				Inhibits NADPH-linked aldehydereductase [necessary for gammahydroxybutyrate (GHB) synthesis; GHB can induce absences]
Felbamate	++	++	++	++		Decreases Na+ channels, increases $GABA_A$ receptors and reduces NMDA receptors Idiosyncratic toxicity limits use
Gabapentin	+	++	+	+		
Lacosamide	+++					Binds CRMP-2 receptor Possible carbonic anhydrase inhibitor
Lamotrigine	+++	+				
Levetiracetam		+	+	+	+++ (SV2A receptor)	Modulates presynaptic neurotransmitter release by SV2A receptor binding
Oxcarbazepine	+++	+				
Perampanel				+++		
Phenytoin	+++					

Table 2 continued: Proposed Pharmacological Targets for ASMs

Drug	Sodium channels	Calcium channels/ currents	GABA-mediated inhibition	Glutamate receptors	Presynaptic release machinery	Other
Pregabalin		++				
Rufinamide	++					+?
Stiripentol			+++			
Tiagabine			+++			
Topiramate	++	++	++	++		+weak carbonic anhydrase inhibition Blocks voltage dependent Na^+ channels, decreases AMPA/kainate receptors and potentiates activity of $GABA_A$ receptors
Valproate	+++	+ (Modulates T-type currents)	+	+		Increases GABA levels through activation of glutamic acid decarboxylase (GAD) and inhibition of GABA transaminase; increases blockade of voltage dependent Na+ channels, and reduces NMDA receptors
Vigabatrin			+++			Inhibits GABA metabolism
Zonisamide	+++	++ (Modulates T-type currents)				++ Facilitates catecholaminergic and dopaminergic neurotransmission; + weak carbonic anhydrase inhibition

+++ Primary target; ++ Probable target; + Possible target

3.2 ASM interactions and interactions between ASMs and other drugs

This is a potentially complex component of polytherapy (Zaccara and Perucca 2014). Please refer to Section 6 in *Clinical Guidelines for the Management of Epilepsy in Adults and Children*. For new ASMs, routine drug-level monitoring has not been demonstrated to be of any value. In selected patients, drug-level monitoring may be of value. Examples include renal failure, dialysis, to assess compliance and in patients who are pregnant (Striano et al. 2008). The following clinically relevant interactions should be considered for drug-resistant epilepsy:

- Valproate decreases clearance of rufinamide, phenobarbital and carbamazepine
- Phenytoin and phenobarbital increase clearance of each other (important for neonates)
- Autoinduction of carbamazepine metabolism
- Stiripentol increase concentration of clobazam
- Valproate decreases clearance of lamotrigine

3.3 Treatment of childhood epilepsy syndromes

For the common medical refractory childhood epilepsy syndromes the following suggestions are made (Hussain and Sankar 2011; Wirrell et al., 2017):

Infantile spasms: Adrenocorticotropic hormone, high dose prednisone/prednisolone, vigabatrin

Lennox-Gastaut Syndrome: Valproic acid should be considered as a first-line treatment, but should be used with caution in women and girls of childbearing age (see Section 8.4 in *Guidelines for Management of Epilepsy in Adults and Children*). Lamotrigine may be considered as a second-line treatment, but can exacerbate myoclonic seizures in select patients. If second-line treatment is ineffective, third-line treatment options include clobazam, cannabidiol in combination with clobazam, rufinamide and topiramate (NICE, 2021). Felbamate, levetiracetam, brivaracetam and perampanel may also be effective, although felbamate is not commonly used due to the risk of aplastic anemia and hepatic failure (Strzelczyk & Schubert-Bast, 2021).

Dravet Syndrome (previously known as Severe Myoclonic Epilepsy of Infancy): Because this is a SCN1A-based voltage-gated sodium channel disorder, ASMs targeting these should not be used. A recent international consensus panel suggests valproic acid is an appropriate first-line drug and clobazam can be considered as either the initial or second ASM. Fenfluramine, stiripentol or clobazam are recommended as second-line treatments. Pharmaceutical-grade cannabidiol is indicated as the third-line treatment, with topiramate or ketogenic diet therapy considered fourth-line treatments (Wirrell et al., 2022). Carbamazepine, oxcarbazepine, lamotrigine and phenytoin should be avoided; however, phenytoin may be helpful for status epilepticus (Wirrell et al., 2022).

Developmental and/or epileptic encephalopathy with spike-wave activation in sleep (formerly Landau-Kleffner Syndrome/Electrical Status Epilepticus in Sleep/Continuous spike-wave during slow wave sleep): The most commonly used treatments are valproic acid, levetiracetam, benzodiazepines, ethosuximide, topiramate, sulthiame, steroids and surgery (in those who are eligible). Among ASMs, valproic acid is considered a first-line treatment, although ASM treatment appears to be less effective (Van den Munckhof et al. 2015). If valproic acid is unsuccessful, nocturnal diazepam may be initiated, followed by prednisolone as a third-line treatment (RamachandranNair 2020).

3.4 Cannabis

Medical cannabis was first legalized in Canada in 2001. In 2013, the Marijuana for Medical Purposes Regulation (MMPR) was introduced and consisted of a program in which registered patients were authorized by health care practitioners to access dry flower which they obtained from Canadian licensed producers. The Access to Cannabis for Medical Purposes Regulations (ACMPR) replaced the MMPR in 2016 and permitted access to medical cannabis products beyond dry flower, such as oils. In 2018, the Cannabis Act was passed legalizing cannabis for recreational purposes. The MMPR was rolled into the Cannabis Act remaining as a separate mechanism by which patients, including children, could access cannabis under the authorization of a physician or nurse practitioner.

The *Cannabis sativa* plant contains close to 500 compounds, of which the two principal components are the cannabinoids delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Likely due to CBD's non-euphoric property and historical data from the 1980s signaling positive effects on seizures, much of the research in the last two decades has focused on this cannabinoid. Currently, the only plant-derived cannabis product approved by Health Canada is Sativex (Nabiximols) which is an oromucosal spray consisting of a balanced mixture in a 2.7mg/ml THC to 2.5mg/ml CBD proportion. It is indicated as adjunctive treatment for symptomatic relief of spasticity in adult patients with multiple sclerosis who have not responded adequately to other therapies. All other plant-derived medical cannabis products have no indication for approved use by Health Canada. Synthetic cannabinoids such as Nabilone (a THC analogue) are approved for the treatment of severe nausea and vomiting in the context of chemotherapy treatment. There are no official Health Canada recommendations nor approvals for the treatment of seizures with cannabis.

An increasing body of literature suggests potential therapeutic use of medical cannabis in epilepsy. RCTs and open-label studies in recent years have demonstrated the effectiveness of CBD to treat drug-resistant childhood-onset epilepsy, specifically Dravet syndrome (DS), Lennox-Gastaut syndrome (LGS), and tuberous sclerosis complex (TSC). Pivotal trials using CBD as an add-on therapy have shown a reduction in seizure frequency for all seizure types, including convulsive seizures, drop seizures and focal seizures, particularly in the presence of clobazam (CLB) (Devinsky et al. 2017, Thiele et al., 2018, Devinsky et al. 2018, Thiele et al. 2021). Epidiolex (GW Pharma), a purified CBD formulation, has been approved in the United States (US) and Europe (in combination with CLB) as an add-on treatment for DS, LGS and TS (US only) in people 2 years of age and older who have failed two appropriate ASM trials. Currently in Canada, although purified CBD formulations are available, most formulations are typically CBD-rich extracts which contain some amount of THC and other cannabinoids.

Although no single mechanism of antiseizure action has been identified, potential pathways include: (Laprarie et al., 2015; Senn et al, 2020; Franco et al., 2021)

i. Antagonism of G protein-coupled receptor 55 (GPR55)
ii. Desensitization of transient receptor potential vanilloid type 1 (TRPV1) channels
iii. Potentiation of adenosine-mediated signaling through inhibition of the equilibrative nucleoside transporter 1 (ENT-1)
iv. Potentiation of γ-aminobutyric acid (GABA) transmission
v. Negative allosteric modulation of the cannabinoid receptor type 1 (CB1)

CBD has a clinically significant interaction with CLB that involves an elevation of plasma levels of the active metabolite N-desmethyl-clobazam. Analysis from direct comparisons have found antiseizure effects from CBD alone, but propose that outcomes may be superior in patients with CLB co-medication (Bialer & Perucca, 2020).

3.4.1 Adverse effects and drug interactions

Adverse effects of CBD include somnolence (particularly in children taking CLB), gastrointestinal disturbances, decreased appetite, and transaminase elevations (in those concurrently using valproate). Knowledge of long-term side effects is lacking, including teratogenicity.

In vitro studies suggest CBD is a strong inhibitor of CYP3A4 and CYP2C19 activity, which likely mediates the rise in CLB levels seen with CBD co-administration. Other pharmacodynamic and pharmacokinetic interactions have been reported with multiple ASMs, including zonisamide, eslicarbazepine, topiramate, and rufinamide and thus, drug level monitoring of ASMs with known interactions is important when prescribing CBD.

Common adverse effects of THC at low to moderate doses include somnolence, dizziness, nausea and forgetfulness. At high doses of THC, increased heart rate, excessive sweating, feelings of paranoia and anxiety can result (Soltesz et al., 2015).

3.4.2 Dosing and formulations

Cannabis oil is typically administered twice per day given the half-lives of CBD and THC. Oils can be taken with high fat foods to maximize absorption.

For formulations that contain purified CBD and no THC (e.g. 0:25, 0:50, etc), dosing information is informed mainly by randomized control trials, some open-label studies and real world evidence. These data show that ranges of 5-20 mg/kg/day or 300 – 600 mg of CBD per day are tolerable with no significant or mild side effects (Devinsky et al. 2017, Thiele et al., 2018, Devinsky et al. 2018, Thiele et al. 2021). Given the absence of THC in these formulations, doses can be elevated beyond 20 mg/kg/day and 600 mg per day; however, if no effect is seen at these doses, it is not common that an effect will result beyond these limits.

For purified CBD in children (<30kg): Start with 2 mg/kg/day and titrate to target dose of 15 mg/kg/day (minimum 10; maximum 30 mg/kg/day). If no effect on seizures by 20 mg/kg/day, it is unlikely that the patient will respond to higher doses.

For purified CBD in children (≥30kg): Start with 50 mg per day and titrate to target dose of 450 mg/day (minimum 300; maximum 600 mg/day). If no effect on seizures by 500 mg/day, it is unlikely that the patient will respond to higher doses.

For formulations that contain a combination of CBD and THC (e.g. 1:20, 2:50, etc), dosing information is informed by open-label studies and real world evidence. These data show that ranges of 0.5 – 0.7 mg/kg/day or 15 – 20 mg of THC per day are tolerable with no significant side effects when utilized in the context of CBD (Huntsman et al 2019). Therefore, target doses should focus on the amount of CBD per day while considering the known tolerable ranges of THC which will be dictated by the ratio of THC:CBD in the oil used.

For CBD-rich extracts in children (<30kg): Start with 2 mg/kg/day of CBD and titrate to target dose of 10 mg/kg/day of CBD (minimum 5 mg/kg/day CBD; maximum 15 mg/kg/day CBD). If no effect on seizures by 12-13 mg/kg/day, it is unlikely that the patient will respond to higher doses.

For CBD-rich extracts in children (≥30kg): Start with 60 mg/day of CBD and titrate to target dose of 300 mg/day of CBD (minimum 150 mg/day; maximum 450 mg/day). If no effect on seizures by 350-400 mg/day of CBD, it is unlikely that the patient will respond to higher doses.

Note: a minority of patients respond at low doses of CBD and THC. Caregivers and patients should be informed to slow or stop titration if significant effect is observed at doses lower than the above recommended targets.

Recommendations:

- Any neurologist/epileptologist considering authorizing cannabis should be aware of different products available in Canada and able to differentiate between purified CBD oils and cannabinoid-rich extracts (e.g. CBD-rich extract 1:20).
- Purified CBD oil without THC may be considered as an add-on treatment for patients with Dravet Syndrome (DS), Lennox-Gastaut Syndrome (LGS) or tuberous sclerosis complex (TSC) when those patients have failed two appropriately prescribed ASMs.
- The management of medical cannabis in children with LGS, DS, and TSC or any other drug-resistant epilepsy should be guided by an epileptologist.

- Medical cannabis containing THC is currently considered an add-on treatment for DRE by practitioners with experience in prescribing medical cannabis. Addition of THC should be guided by a neurologist or epileptologist with experience authorizing and utilizing medical cannabis in the epilepsy population.

- Medical cannabis products should be procured from a Health Canada licensed producer.

- Appropriate baseline and follow-up assessments should be carried out, including bloodwork, ECG and seizure diary.

- Interactions with concurrent ASMs should be noted and monitored with baseline drug levels and follow-up levels as clinically indicated.

- Cannabis use is contraindicated in patients with acute psychosis. Relative contraindications include severe cardiovascular, immunological, liver or kidney disease, or arrhythmia. Specialist opinions should be sought as clinically indicated.

- Patients should be made aware that it is illegal to transport any medical cannabis products including CBD-containing products across the Canadian border and into other countries even if cannabis is legal in these destinations.

See Appendix 8 for more information on obtaining cannabis for medical use.

3.5 Immunotherapy

The main treatment options other than ASMs include medications used when the immune system is involved.

Evidence that the immune system is involved in the pathogenesis of epilepsy, particularly drug-resistant epilepsy, has given rise to the use of adjunctive immunotherapy to slow or change the epileptogenic process. Treatments include immunoglobulins, corticosteroids, plasmapheresis and monoclonal antibodies such as rituximab and natalizumab. There are limited data for these treatments outside of specific epileptic encephalopathies such as West syndrome, Rasmussen's encephalitis (RE), Landau Kleffner Syndrome and autoimmune encephalitis such as anti-NMDA encephalitis.

Corticosteroids form one of the main treatment options. Corticosteroids cause immunosuppression by decreasing the function and numbers of lymphocytes, including both B cells and T cells. By inhibiting a critical transcription factor involved in the synthesis of many mediators (i.e., cytokines) and proteins (i.e., adhesion proteins) that promote an immune response, they blunt the capacity of the immune system to mount a response.

Corticosteroids have an anti-inflammatory effect by preventing the formation of prostaglandins and leukotrienes, two main factors in inflammation. This is mediated by the release of lipocortin which by inhibition of phospholipase A2 reduces arachidonic acid release. Corticosteroids have been used as therapy in many epileptic syndromes including infantile spasms, an age- specific epilepsy syndrome associated with epileptic spasms, in many cases with neurodevelopmental regression and an EEG finding of hypsarrhythmia (West Syndrome) and more recently in autoimmune encephalitis.

3.5.1 Infantile spasms (IS)

First-line treatments for IS include low or high dose adrenocorticotropic hormone (ACTH), prednisolone, and vigabatrin. A recent comparative study provides class III evidence that for children with new-onset IS, ACTH or oral steroids are superior to nonstandard therapies (ASMs or diet therapy). When used, vigabatrin appears to work best for children with tuberous sclerosis complex (TSC) (Grinspan et al., 2021). As ACTH is not available in Ontario, vigabatrin is usually the first-line treatment, followed by prednisolone. High-dose oral prednisolone (8 mg/kg/day) may be a reasonable alternative to ACTH given the ease of administration, lower cost and similar effectiveness/adverse effect profile (Al-Shehhi et al., 2022). Treatment with ACTH/oral steroids may result in a better long-term neurodevelopmental outcome than treatment with vigabatrin in children with epileptic spasms due to to unknown etiologies (Wilmhurst et al., 2015).

Early intervention is critical, as delayed diagnosis and treatment can result in lasting deleterious deficits in development and cognition (Patel et al., 2018).

3.5.2. Rasmussen's encephalitis (RE)

Steroids are also used in RE, which is a rare, sporadic but potentially severe immune-mediated brain disorder leading to unilateral hemispheric atrophy, associated progressive neurological dysfunction and poorly controlled seizures. Despite its autoimmune pathogenesis, the only definitive treatment is functional hemispherectomy (Orsini et al., 2020). A pharmacological approach with agents acting on the immune system, and in particular on T-cell immunity, is a preferable strategy at an early stage of the disease or in patients with slow disease progression and mild deficits and/or who are not eligible for hemispheric surgery (Lagarde et al. 2022).

Prednisolone/prednisone started at a high dose and then slowly tapered down has been reported to have beneficial effects on seizures and neurological functions in several case series in patients with RE (Class IV evidence), particularly when started early on in the course (Chinchilla et al. 1994; Hart et al. 1994; Granata et al. 2003). For long- term steroid therapy, it has been recommended to start with boluses of intravenous methylprednisolone [e.g. 400 mg/m2/day (Hart et al. 1994) or, in children, 20 mg/kg/day (Granata et al. 2003)] and then to introduce 1–2 mg/kg/day oral prednisolone or prednisone (Hart et al. 1994; Granata et al. 2003). This dose should be slowly reduced, ideally to a dose below the threshold of Cushing's syndrome.

Bahi-Buisson et al. confirmed steroid treatment can be useful when given early on in the course of RE, but they found that long term relapse can occur among the good responders requiring delayed hemispheric disconnection (Bahi-Buisson et al., 2007). Long-term use of corticosteroids is also limited by side effects, including Cushing's syndrome, osteoporosis, hypertension, and infection.

Immunoglobulins have also been used in RE as well as autoimmune encephalitis (Granata et al. 1994; Hart et al. 2003). IVIg is a purified blood product pooled from many human donors composed mainly of IgG and some IgA. The precise mode of action of this product is unclear. Several studies have shown efficacy in treating patients with immunodeficiency. The use in patients with epilepsy has increased given the identification of immune mediated epilepsy but Cochrane reviews show no randomized evidence outside of specific syndromes such as anti-NMDA and Landau Kleffner (Geng et al. 2013; Gayatri et al. 2007). The efficacy of IVIg to reduce seizures in RE appears to be lower than for corticosteroids. Thus, corticosteroids may be proposed as the first-line treatment, with IVIg being reserved for cases where corticosteroids fail and before starting another long-term treatment. This does not rule out long-term use of IVIg on a case-by-case basis, in cases of very good response, because of better long-term tolerance than corticosteroids (despite the time-consuming nature of their regular administration for the patient) (Lagarde et al., 2022).

3.5.3 Autoimmune epilepsy (AE)

Steroids, immunoglobulins and other anti-inflammatory agents are also increasingly used in immune epilepsy. If these agents are to be used it would be important to potential patients who have an immune basis for their seizures because adjunctive immunotherapy may slow, halt, or even reverse the epileptogenic process. In 2017, the ILAE added autoimmune epilepsy to their classification system, defining an immune etiology of seizures where there is evidence of autoimmune-mediated central nervous system inflammation. However, the definition continues to evolve, with some proposing a distinction between acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy (Steriade et al., 2020). Accurate and early diagnosis along with appropriate treatment of autoimmune epilepsy can significantly improve clinical outcomes, as affected patients often have seizures that are highly resistant to ASMs but respond favourably to immunotherapy.

Discovery of neural autoantibodies is central to the recognition of an immune-mediated epilepsy (Quek & O'Toole, 2018).

The more frequently identified antibodies associated with autoimmune epilepsy are directed against the VGKC complex (specifically LGI1 and CASPR2), glutamic acid decarboxylase 65 (GAD65), and NMDAR antigens. NMDAR, LGI1, CASPR2, AMPAR, $GABA_AR$, and $GABA_BR$ antibodies are particularly associated with encephalitis and seizures. The presence of these neural autoantibodies is highly suspicious for autoimmune epilepsy and predicts likely response to immunotherapy. Rarely, nuclear or cytoplasmic paraneoplastic antibodies have been identified in patients with autoimmune epilepsy (ANNA-1, ANNA-2, amphiphysin, CRMP-5, and Ma/Ta antibodies). Although antibodies are detectable in up to 35% of patients with epilepsy, testing is problematic as not all autoimmune epilepsies will be antibody-mediated and not all antibodies are known (Tan et al., 2021). McGinty et al. (2021) suggest that detection of neuronal surface-directed antibodies in patients with new-onset seizures, but without features of AE, should not alter current clinical management, and thus a combination of clinical diagnosis and antibody testing should be used to guide treatment.

Diagnosis: (Quek & O'Toole, 2018)

The diagnosis of autoimmune epilepsy can be confirmed based on a triad of clinical features, neural autoantibody detection, and response to immunotherapy. Features include subacute onset (days, weeks) of epilepsy of unknown etiology, unusually high seizure frequency, and resistance to ASMs. Patients with a clear seizure etiology (e.g., metabolic, infectious, neoplastic, or structural causes) should be excluded. As with other autoimmune and paraneoplastic disorders, patients may have a strong personal or family history of autoimmunity or cancer.

Seizures are typically focal in origin with motor, sensory, and autonomic manifestations. Neural autoantibodies are detected in 30% of patients, where seizures can be accompanied by peri-ictal autonomic findings (e.g., gastrointestinal manifestations and piloerection). An autoimmune etiology should also be suspected when there is variability in seizure semiology in each individual or a multifocal source of epileptiform discharges. Focal seizures with progression to bilateral tonic clonic, epilepsia partialis continua, and nonconvulsive and convulsive status epilepticus may also occur or coexist in these patients. MRI findings suggestive of inflammation include T2/FLAIR hyperintensities, edema, contrast enhancement on gadolinium studies, and/or restricted diffusion, particularly in mesial temporal structures. CSF inflammation with lymphocytic pleocytosis, elevated protein, CSF-specific oligoclonal bands, and/or a raised CSF IgG index are also supportive. Cancer screening should be always completed if an ongoing cancer is unknown. These investigations include CT thorax-abdominal-pelvis, testicular US or gynecologic examination, and in some cases body PET.

The Antibody Prevalence in Epilepsy and Encephalopathy (APE2) scoring system (Appendix 9) can be used to assist in diagnosis when there is a clinical suspicion of autoimmune epilepsy. In addition, the antibodies contributing to focal epilepsy signs and symptoms (ACES) score (Appendix 10) can help physicians to select patients who should be screened for neuronal antibodies, particularly in cases of chronic and/or focal epilepsy without overt encephalitis. An ACES score ≥2 showed a 100% sensitivity and 84.9% specificity in detecting autoimmune etiology of seizures in patients with focal epilepsy of unknown etiology (de Bruijn et al., 2021).

Treatment: (Quek & O'Toole 2018; Husari & Dubey, 2021)

No randomized clinical control trials on the use of corticosteroids in autoimmune epilepsies have been conducted to date. In an observational, retrospective case series by Quek et al. (2012) of patients with seizure presentation in whom an autoimmune etiology was suspected, neural autoantibodies were identified in 29/32 patients (91%). VGKC complex IgG antibodies were detected in 18/29 (62%), of which 14 were bound to LGI1 (78%), one was bound to Caspr2 and three were of unknown specificity. In addition, GAD65 was found in 7/29 (24%), and CRMP-5 was found in 2/29 (Quek et al. 2012).

In this study, 27 people underwent immunosuppressive treatment that comprised intravenous methylprednisolone alone (IVMP) (n = 12); intravenous immune globulin alone (IVIg) (n = 3); and combinations of IVMP, IVIg, cyclophosphamide, or plasmapheresis (n = 12). In 22/27 patients (81%), this therapeutic trial was positive with 18 patients becoming seizure free for at least 3 months and 4 patients having improved seizure frequency. Early treatment was associated with a favorable outcome ($p<0.05$).

Recommended first-line therapies include high-dose intravenous methylprednisolone (IVMP), intravenous immunoglobulin (IVIg), or plasmapheresis. There are no definitive studies supporting the superiority of one treatment over the other. A typical treatment protocol involves a trial of IVMP for 3-7 days followed by prednisone tapered biweekly, or IVIg bi-weekly for 5 doses, then monthly for 3 doses. After 4 to 6 weeks of a treatment trial, a detailed evaluation for treatment response is performed to decide whether treatment should be continued for an additional interval of time. For patients who show a positive response, IV treatment should be tapered by gradually increasing the interinfusion intervals over 4 to 6 months, as abrupt discontinuation could lead to relapse. Chronic immunosuppression for maintenance immunotherapy (e.g., rituximab, azathioprine or mycophenolate mofetil) to prevent relapses may be considered and initiated while the IV treatment is tapered. The exact duration required for maintenance immunotherapy is not known, although it has been suggested that a trial of immunotherapy withdrawal may be initiated after 2 years of treatment. Rituximab has been used as a second-line treatment, but due to the high cost and potential side effects, it is rarely administered as an outpatient therapy.

The Response to Immunotherapy in Epilepsy and Encephalopathy (RITE2) scoring system (Appendix 9) can be used to predict favourable response to initial immunotherapy and for continued management of therapeutic response.

4. Diet Therapy

Diet therapy for epilepsy is a nonpharmacologic treatment used worldwide for children with drug-resistant epilepsy (Kossoff et al. 2009). Dietary therapies, most often the classic ketogenic diet (KD), have been shown to be particularly beneficial in treating certain specific epilepsy syndromes in children with frequent, drug-resistant seizures. A review of 13 randomized control trials concluded that children given ketogenic diet therapies (KDTs) may be up to three times more likely to achieve seizure freedom and up to six times more likely to experience a 50% or greater reduction in seizure frequency versus those receiving standard care (Cochrane Review, 2020). Dietary therapy has been reported as effective in the treatment of seizures associated with glucose transporter 1 deficiency, pyruvate dehydrogenase deficiency, infantile spasms, absence epilepsy, myoclonic atonic epilepsy (Doose syndrome), Dravet syndrome, tuberous sclerosis complex, mitochondrial disorders, Lennox-Gastaut syndrome, and Rett syndrome (Cervenka & Kossoff 2013; Worden et al., 2020; Kapoor et al., 2021). The common element of these different approaches is variable reduction in the amount of carbohydrate with appropriate increase in fat.

Diets that produce a state of ketosis are referred to as “ketogenic” (Cervenka & Kossoff 2013). When deprived of glucose through restriction of carbohydrate intake, the human body begins metabolizing fat. In doing so, ketone bodies (acetoacetate, acetone, and hydroxybutyrate) are produced. There is no direct correlation between seizure reduction and the degree of either acidosis or ketosis achieved. The mechanisms of action are much more complicated and may involve alterations in mitochondrial function, direct effects of ketone bodies on neuronal function and neurotransmitter release, effects on GABA and glutamate metabolism, activation of ion channels and inhibitory receptors, increased adenosine levels, glycolytic restriction/diversion, antiepileptic effects of fatty acids, and/or glucose stabilization (Cervenka & Kossoff 2013: Rogawski et al., 2016). Limited data are available for the adult population.

4.1 Types of ketogenic diets

4.1.1 Classic KD

In the classic KD, food-based long-chain triglycerides (LCTs) are the main source of fat. Typically, 87-90% of calories are from fat, with carbohydrate and protein intake limited to 10-30% of calories combined. The diet is initiated on an inpatient basis and is restrictive, as all diet components are weighed/measured with strict control of daily calorie intake. The ketogenic ratio is defined as the ratio of grams of fat to grams of carbohydrate plus protein. For example, the common 4:1 ratio classic KD contains 4 grams of fat for every 1 gram of protein and carbohydrate combined. A 3:1 or lower ratio can be used alternatively to increase protein or carbohydrate intake (Kossoff et al., 2018). There is no evidence to support the use of fasting before diet initiation. There is no scientific evidence to suggest that fluid restriction is needed or beneficial. Because of concerns of possible nephrolithiasis, most centers no longer restrict fluids. In humans, no study to date has shown a benefit of calorie restriction (Wirrell 2008). While excessive weight gain is perceived to correlate with poorer efficacy, no link was found between either ideal body mass index or change in body mass index over time and seizure control in children treated with the KD (Hamdy et al. 2007). The classic KD can be provided to patients through food or formula by enteral tube feeding or by mouth, or a combination of food and formula.

4.1.2 Medium Chain Triglyceride (MCT) diet

Medium-chain triglycerides (C6-C12), delivered as an oil, are the main sources of fat in this diet. They require little to no pancreatic lipase for digestion and are quickly hydrolyzed into medium-chain fatty acids. The absorption of MCTs is faster than LCTs, yielding a quick and efficient ketone source for energy. Since MCTs are more ketogenic than LCTs, the addition of MCT oil allows for more carbohydrate and is thus more palatable than the classic KD (Huttenlocher et al. 1971). In the traditional MCT diet, 60% of its energy is derived from MCT. A modified MCT diet is used in some centres, for example, using 30% of energy from MCT and an additional 30% from long-chain fatty acids (Neal et al., 2009). MCT oil can be given as coconut oil or as an emulsion, and should be included in all meals when used (Kossoff et al., 2018). MCT oil in variable amounts can be used along with any type of diet therapy in the treatment of epilepsy. It is successfully used with limited side effects when the diet is administered carefully (Liu 2008; Neal et al., 2009). Better toleration may be achieved using less MCT with each meal but providing more meals per day. MCT oil consumption may also cause throat irritation due to the presence of C6 (caproic acid) (Kossoff et al., 2018).

4.1.3 Modified Atkin's Diet (MAD)

The modified Atkin's diet (MAD) provides a more palatable and less restrictive outpatient-initiated dietary treatment for older children and adults (Kossoff et al. 2006; Kang et al. 2007; Kossoff and Dorward 2008). The MAD typically provides approximately a 1:1–1.5:1 ketogenic ratio, but no set ratio is mandated (Kossoff et al., 2018). In children, carbohydrates (excluding the fibre content) are limited to 10-20 g/day. In adults, carbohydrates (excluding the fibre content) are limited to 15-30 g/day as tolerated based on seizure control. There is no calorie, protein, fat or fluid restriction. Fat intake from food is not defined but rather encouraged (Kossoff et al. 2013). As precise calculations are not required, the MAD may be ideal in settings where access to trained dietitians is limited (Kossoff et al., 2018). Although adherence to the MAD is increased in adults and adolescents, current recommendations suggest the classic KD rather than MAD should be offered to children <2 years of age (Kossoff et al., 2018).

The rationale for choosing 10-20g as the initial daily carbohydrate intake in MAD is unclear. Centers vary in their practice of choosing the initial carbohydrate amount or its titration in MAD. A recent survey among dietitians in the United Kingdom (UK) reported 72% of centers advised patients to make initial dietary modifications before commencing a modified diet. These modifications included reducing dietary intake of high sugar foods and overall carbohydrates over a 4–6-week period (Lord & Magrath 2010). Though all UK centers provided a specific carbohydrate target, this was based upon a predetermined weight between 15 and 30g/day in 67% of centers and

based upon 5% of the estimated total energy requirements in 28% of centers. The survey also mentioned one center calculated carbohydrates to provide between 10% and 20% of estimated total energy. This means, for an older child requiring daily 1500 calories, daily carbohydrate intake would be 37.5-75 grams. Authors from South Korea reported a different method of implementing MAD. Carbohydrates were restricted to 10 g/day initially, but were allowed to be increased by 5 g/day to a maximum of 10% carbohydrates per day by weight at intervals of at least 1 month depending on tolerance (Park et al., 2018). An adult study reported the use of 50 g carbohydrate in their protocol for MAD (Roehl et al., 2019). A practice guideline from Australia indicates carbohydrates are usually reduced over 2 weeks (or longer if there are concerns with low blood sugar) (Modified Atkins Ketogenic Diet: Outpatient model of care for patients with epilepsy, SCH Practice Guideline, 2017). Typically, the ratio is increased over several days/weeks. Recently, a more liberal form of the MAD with slow reduction of carbohydrate has been described, allowing for less carbohydrate restriction (i.e. seizures controlled with 45 grams/day of carbohydrate) and increased acceptability of the diet in a child with GLUT-1 transporter deficiency (Gauthier et al., 2020).

In contrast to the popular Atkin's diet, weight loss is not the goal of the modified Atkin's diet for seizures, unless nutritionally indicated (Kossoff & Dorward, 2008).

4.1.4 Low Glycemic Index Treatment (LGIT)

The glycemic index (GI) is a measure of how much a particular food will elevate the blood glucose compared to glucose (equivalent amount) (Jenkins et al. 1981). As with the MAD, LGIT is typically initiated on an outpatient basis. LGIT allows a more liberal amount of carbohydrate, restricted to carbohydrates with a glycemic index of less than 50 (Pfeifer and Thiele 2005).

LGIT reduces the blood glucose by altering the quality and the types of carbohydrates in the diet. It is hypothesized that low GI carbohydrates produce a smaller increase in blood glucose and thereby less variability in blood glucose levels throughout the day. These metabolic changes might have anticonvulsant effect by themselves (Valencia et al. 2002).

Typically, the LGIT consists of 60–70% fat, 20–30% protein and 10% carbohydrates with low glycemic indices (GI < 50). The usual carbohydrate intake per day is 40-60g (Pfeifer and Thiele 2005; Coppola et al. 2011). Sondhi et al. (2020) compared the use of classic KD, MAD and LGIT in an RCT of 158 children with DRE. At 24 weeks, the median reduction in seizure frequency was similar in all treatment groups. Adverse effects were similar in the classic KD and MAD groups but were significantly reduced in the LGIT group. Similarly, in an RCT comparing the efficacy of the MAD and LGIT, Gupta et al. (2021) demonstrated that at 12 weeks, seizure freedom, 90% seizure reduction rates and 50% seizure reduction rates were similar between the LGIT and MAD groups.

4.2 Individualized modifications to diet

There is evidence to suggest all forms of diet therapy mentioned above help control seizures. The exact mechanism of action is unclear. In order to make the diet therapy less onerous and more palatable (less weighing and measuring, less restriction on food choices, and gradual introduction of diet), a regimen that uses principles of MAD, LGIT, MCT, and outpatient initiation can be used. Each center should have protocols, whether for child or adult, that include appropriate investigations prior to initiating a diet therapy and for monitoring during the course of treatment (see Appendices 6 and 7).

Rapid lowering of daily carbohydrate intake can be difficult to implement in some patients on MAD and LGIT diet. A more gradual reduction in the amount of carbohydrates consumed can be undertaken over days to weeks depending on tolerability, palatability and seizure control. This is similar to the practice of gradual initiation of the classic KD. For a given ratio of classic KD, a further reduction in carbohydrate is possible by increasing the protein intake without changing the amount of fat. Variable amounts of MCT oil can be added to any type of diet to increase the ketogenic potential. Adverse effects of KDT most commonly involve the gastrointestinal system and are seen during the first few weeks of initiation.

Constipation, emesis, and abdominal pain may occur in up to 50% of children. These effects are usually mild and can be managed with minimal interventions; however, such interventions often remain ongoing, such as management of constipation or the use of proton-pump inhibitors. Possible long-term complications, including effects on growth, vascular outcomes and cardiac abnormalities have not been reviewed systematically (Kossoff et al. 2018).

4.3 Indications and contraindications

Any child with drug-resistant epilepsy who is not a surgical candidate, or who is awaiting surgical evaluations, should be considered for diet therapy, regardless of age, comorbid conditions and cause of the epilepsy. In considering the epilepsy population as a whole, the International Consensus Statement for the Ketogenic Diet (2009) stated that "the KD should be considered in a child who has failed two to three anticonvulsant therapies, regardless of age or gender, and particularly in those with symptomatic generalized epilepsies" (Kossoff et al. 2009). KDT can also be used for the management of adults with epilepsy (see section 4.7).

Conditions and syndromes for which KDT has been consistently reported as beneficial or moderately beneficial are listed in Tables 3 and 4. KDT should be considered the treatment of choice for Glut1 deficiency syndrome (Glut1DS) and pyruvate dehydrogenase deficiency (PDHD) (Kossoff et al., 2018; Klepper et al., 2020) as ketones can bypass the metabolic deficits and serve as an alternative cerebral fuel source.

Absolute contraindications for the use of KDT include carnitine deficiency (primary), carnitine palmitoyltransferase (CPT) I or II deficiency, carnitine translocase deficiency, β-oxidation defects, medium-chain acyl dehydrogenase deficiency (MCAD), long-chain acyl dehydrogenase deficiency (LCAD), short-chain acyl dehydrogenase deficiency (SCAD), long-chain 3-hydroxyacyl-CoA deficiency, medium-chain 3-hydroxyacyl-CoA deficiency, pyruvate carboxylase deficiency, and porphyria (Kossoff et al., 2018).

Table 3: Conditions and syndromes for which KDT has been consistently reported as more beneficial (>70%) than the average 50% KDT response (defined as >50% seizure reduction) (Kossoff et al., 2018)

- Angelman syndrome
- Complex 1 mitochondrial disorders
- Dravet syndrome
- Epilepsy with myoclonic–atonic seizures (Doose syndrome)
- Glucose transporter protein 1 (GLUT-1) deficiency syndrome (GLUT1DS)
- Febrile infection–related epilepsy syndrome (FIRES)
- Formula-fed (solely) children or infants
- Infantile spasms
- Ohtahara syndrome
- Pyruvate dehydrogenase deficiency (PDHD)
- Super-refractory status epilepticus
- Tuberous sclerosis complex

Table 4: Conditions in which KDT has been reported as moderately beneficial (not better than the average dietary therapy response, or in limited single-center case reports) (Kossoff et al., 2018)

- Adenylosuccinate lyase deficiency
- CDKL5 encephalopathy
- Childhood absence epilepsy
- Cortical malformations
- Epilepsy of infancy with migrating focal seizures
- Epileptic encephalopathy with continuous spike-and-wave during sleep
- Glycogenosis type V
- Juvenile myoclonic epilepsy
- Lafora body disease
- Landau-Kleffner syndrome
- Lennox-Gastaut syndrome
- Phosphofructokinase deficiency
- Rett syndrome
- Subacute sclerosing panencephalitis (SSPE)

Relative contraindications include inability to maintain adequate nutrition, surgical focus identified by neuroimaging and video EEG monitoring, parent or caregiver noncompliance, and concurrent use of propofol (Kossoff et al. 2018). Children who require thickened fluids by mouth due to difficulties with swallowing cannot use the ketogenic diet, as thickening agents are not compatible with the diet. In those children, tube feeding is an alternative that may be considered. There is little evidence of any consistent beneficial interactions between KDT and ASMs. Conversely, there are no particular ASMs that need to be avoided with KDT.

4.4 Diet initiation

Each center should have a protocol for diet initiation and follow-up (see Appendix 7). The choice of KDT should be based on the personal and family situation of each individual patient and the expertise of the diet center rather than perceived efficacy (Kossoff et al., 2018).

3.4.1 Inpatient initiation

All variations of diet therapy for epilepsy can be initiated through an inpatient admission. However, MAD and LGIT are typically initiated on an outpatient basis. The diet therapy will require a titration to reach the goal prescription. This titration can involve adjustments in daily calories, ketogenic ratios or macronutrient energy distributions. Careful daily monitoring for metabolic abnormalities (e.g. acidosis, hypoglycemia, excessive ketosis) and associated symptoms such as vomiting will be required. The purpose of the inpatient admission is to reach the initial goal diet prescription more quickly. If the patient is tolerating this goal prescription, they can be discharged home. Seizure control may not yet be optimized therefore further adjustments to the diet prescription can be made as an outpatient.

3.4.2 Outpatient initiation

MAD and LGIT diets usually begin on an outpatient basis. Many centers use outpatient initiation methods for classic KD and MCT KD as well (Vaisleib II et al., 2004). The variations of the diet therapies for epilepsy can also be implemented as an outpatient. There are two types of practices. Common practice is rapid titration of diet to a higher ratio within 3-5 days, which can be useful in some settings, such as febrile infection-related epilepsy syndrome (FIRES). However, it is possible that this approach results in some patients receiving a higher ratio than they require. Many patients achieve seizure control with lower ketogenic ratios, with improved tolerability of the diet. However, in a minority, higher ratios result in better efficacy (Kossoff and McGrogan 2005; Seo et al. 2007; Wirrell 2008). Alternative approaches include: 1) inpatient initiation on a lower ratio with the goal to find a diet ratio that is tolerated or 2) an outpatient initiation with the same approach, which can be used for children who are more medically stable. Depending on the tolerability and desired seizure control, the ratio can be increased gradually (Roehl & Sewak, 2017; van der Louw et al., 2019). Typically, the ratio is advanced over several days or weeks. Good seizure control has been achieved with lower KD ratios, suggesting that many patients who are arbitrarily put on higher ratios by rapid inpatient or outpatient titration may have had good seizure control at lower ratios had there been a slower titration of the diet.

4.5 Concurrent ASMs

There is little evidence to suggest either a beneficial or detrimental interaction between KDT and ASMs. ASMs may be reduced after 1 month if KDT is successful, although gradual tapering is advised when reducing phenobarbital or benzodiazepines due to a possible risk of seizure worsening on KDT (Kossoff et al., 2018).

4.6 Supplementation (Kossoff et al., 2018)

Multivitamin supplementation is essential, especially for B vitamins. Carbohydrate-free vitamin and mineral and products should be used. KD foods have insufficient Vitamin D and calcium, and these should be provided at the recommended daily allowance. Due to a potential link to cardiomyopathy, selenium levels should be checked periodically to determine if additional supplementation is needed beyond the standard multivitamin.

Supplementation for magnesium, zinc, phosphorus, iron, and copper is also recommended. Currently, there is no evidence to support a beneficial effect of additional vitamin, probiotic or omega-3 fatty acid supplements. Oral citrates may be used to reduce the risk of kidney stones. Constipation and GI dysmotility are common side effects of KDT, particularly the classic KD. Prevention techniques include higher fibre vegetables, sufficient fluid intake and carbohydrate-free laxatives if needed. Carnitine supplementation is recommended only if levels are low or children become symptomatic.

4.7 Diet therapy in adults

KDT for epilepsy can be used safely in the adult and adolescent populations, with response rates similar to those seen in children. Patients with symptomatic generalized epilepsy may be particularly good candidates for this type of dietary treatment (Nei et al. 2014). KDTs are appropriate to offer to adults with seizure types and epilepsy syndromes for which these treatments are known to be effective in children, including tuberous sclerosis complex, Rett syndrome, LGS, Glut1DS, genetic generalized epilepsies, and focal epilepsies due to underlying migrational disorders and resistant to ASMs. Contraindications to KDT in adults are shown in Table 5.

As with children, adults with drug-resistant focal epilepsy should be offered surgical evaluation first due to the higher anticipated rate of seizure freedom (Stainman et al., 2007). However, some patients may prefer to avoid surgery despite being a surgical candidate. All KD therapies may be used to treat adults, with the most common being MAD, followed by the classic KD, the modified KD (MKD), and/or LGIT. MCT oil may be used with all forms of KDT (Cervenka et al., 2020). The MKD approach is a hybrid between the MAD and classic KD. In the MKD, fat intake accounts for approximately 75% of calories with carbohydrates providing around 5% of energy requirements. A moderate, rather than unrestricted intake of protein is encouraged. The classic KD is used for adults receiving the majority of their nutrition through enteral feedings. Liquid or powdered ketogenic formulas can meet an adult's nutritional requirements, although they may require additional supplements depending on their medical needs.

For adults who are considering dietary therapy for the first time, are independent, employed, and care for dependent children/other family members, MAD can provide a less restrictive and less time- consuming alternative to the classic KD (Cervenka et al. 2013). Adverse effects that may occur in the first few weeks of diet initiation include fatigue, thirst, irritability, hunger and altered bowel habits (particularly constipation).

Recommendations: (Cervenka et al., 2020)

- All adults on oral food based KDTs should be advised to increase their fluid consumption and take a multivitamin, mineral, and trace element supplement, that meets recommended daily allowances. Additional vitamin D3 and calcium supplementation are of likely value to adults as well. Supplemental magnesium, carnitine, anti-emetics, citrates, and antacids are recommended in symptomatic or at-risk patients.

- Biochemical studies are recommended prior to the initiation of KDTs in adults. Metabolic screening may not be necessary for all adults pre-KDT, given that many contraindicated disorders present in infancy and early childhood. Regular outpatient follow-up and biochemical monitoring (CBC, CMP, fasting lipid profile, vitamin D level) are important to identify and manage possible KDT complications. Serial bone mineral density scans beginning within 5 years of initiating KDT may be an additional consideration for adults with multiple associated risk factors.

- Ketone monitoring (blood β-hydroxybutyrate or urine acetoacetate) is recommended during the early months of KDT as an objective measure of KDT compliance and biochemical response. However, diet adjustments should focus on optimizing the treatment response, minimizing side effects and maximizing sustainability.

Table 5: Absolute and relative contraindications to KDTs in adults (Cervenka et al., 2020)
Absolute contraindications (* symptoms typically present in childhood and adolescence)
Carnitine deficiency (primary)*
Carnitine palmitoyltransferase I or II deficiency* (myopathic form may present in adolescence)
Carnitine translocase deficiency*
Mitochondrial fatty acid β-Oxidation disorders*
Short-chain acyl dehydrogenase deficiency (SCAD)*
Medium-chain acyl dehydrogenase deficiency (MCAD)*
Long-chain acyl dehydrogenase deficiency (LCAD)*
Very Long-chain acyl dehydrogenase deficiency (VLCAD)*
Medium-chain 3-hydroxyacyl-coenzyme A deficiency (MCHAD)*
Long-chain 3-hydroxyacyl-coenzyme A deficiency (LCHAD)*
Pyruvate carboxylase deficiency*
Pregnancy
Acute pancreatitis
Liver failure
Type 1 diabetes without endocrinology approval and/or supervision*
Porphyria
Relative contraindications
Epilepsy surgery candidate with a clear resectable lesion (unless patient prefers to avoid surgery)
History of pancreatitis
Cholecystectomy
Renal failure
Nephrolithiasis
Type 1 diabetes mellitus with endocrinology approval and/or supervision*
Type 2 diabetes mellitus without endocrinology approval and/or supervision
Osteopenia/ osteoporosis without endocrinology approval or supervision
Hyperlipidemias
History of cardiovascular disease
History of cerebrovascular disease
History of eating disorders, including anorexia nervosa
Severe gastro-esophageal reflux
Inadequate social or care provider support
Poor adherence or difficulty maintaining adequate nutrition

- Initiating KDT with a simpler approach such as MAD and adjusting to include elements of CKD or MCT KD protocols where necessary to optimize the outcome may improve compliance; however, further investigation is warranted. Frequent support from a KDT team is important in the early stages to foster knowledge, skills and confidence in adults managing their KDT.

- A minimum of three months KDT is recommended before any judgement of response is made. The timeframe for KDT discontinuation is dependent on the underlying condition(s) being treated and response to treatment.

4.8 Diet therapy in infants

In the past, the use of KDT has not been recommended for children <2 years of age due to the risk of nutritional inadequacies and potential adverse effects on development. However, KDT is currently used in infants with refractory epilepsy syndromes such as West syndrome, Ohtahara syndrome, epilepsy of infancy with migrating seizures, and infants with focal seizures awaiting epilepsy surgery. As with older children, KDT is the first-line treatment for infants with GLUT1DS and PDHC deficiency. Contraindications to KDT in infants are listed in Table 6.

Recommendations: (Van der Louw et al., 2016)

- All young infants (<12 months) should be admitted to hospital. Diet initiation should be undertaken without fasting and a stepwise start commencing with a 1:1 ratio. A build to a classical KD with 3:1 ratio is recommended, but the ratio can be adjusted based on level of ketosis and tolerance. A KD formula with ratio 3:1 can be used purely or combined with breast milk.
- Energy requirements may be calculated based on individual history and a percentage (75%-100%) of the recommended daily allowance (RDA).
- Protein and fluid intakes based on RDA are advised. Fluid intake should be individually calculated and adjusted frequently based on weight gain and biochemistry results.
- Micronutrient supplementation intake should be calculated individually corresponding to reference intakes for age and weight. When starting to wean off a formula diet, micronutrient intake should be assessed and supplementation commenced as necessary.
- Blood glucose and ketones should be measured twice daily during initiation and daily during the treatment phase.
- The KD should be maintained for 2-3 months to evaluate efficacy, during which time fine-tuning of the diet may be required.

Table 6: Absolute and relative contraindications to KDTs in infants (van der Louw et al., 2016)

Absolute contraindications
Fatty acid oxidation deficiencies (VLCAD, LCHAD, MCAD, OCTN2, CPT1, CPT2)
Pyruvate carboxylase deficiency and other gluconeogenesis defects (fructose 1,6 diphosphatase deficiency)
Glycogen storage diseases (except type 2)
Ketolysis defects
Ketogenesis defects
Porphyria
Prolonged QT syndrome or other cardiac diseases
Liver, kidney or pancreatic insufficiency
Hyperinsulinism
Relative contraindications
Inability to maintain adequate nutrition
Surgical focus identified by neuroimaging and video EEG monitoring
Parent or caregiver non compliance
Growth retardation
Severe gastrointestinal reflux
Familial hypercholesterolemia

5. Neuromodulation

In patients who are not candidates for epilepsy surgery or choose not to undergo surgery, neuromodulation may be used as an alternative treatment for DRE. There is a long history of brain stimulation at a variety of sites; early attempts included cerebellar stimulation for a number of disorders including epilepsy, with results that were not widely accepted. Other targets attempted have included the centro-median and anterior nuclei of the thalamus, the hippocampus, the subthalamic nucleus, and caudate nucleus, with other efforts being directed towards cortical stimulation for epilepsy. However, a number of modalities of electrical stimulation for DRE have support from randomized controlled clinical trials and are accepted as options for use in select cases of DRE, namely vagus nerve stimulation (VNS), deep brain stimulation (DBS) at the anterior nucleus and the centro-median nucleus of the thalamus, and responsive neurostimulation (RNS, not available in Canada), which is applied cortically to the site of seizure onset. Trigeminal nerve stimulation (TNS) has similarly been described and approved for use by Health Canada, but is less commonly used.

Evaluation

Since general neurostimulation devices are less effective than epilepsy surgery, patients with DRE should not be considered for such devices until more effective treatment options such as effective surgical resections have been considered.

An appropriate comprehensive assessment at a surgical centre would include video-EEG monitoring, and evaluation by neuroradiology, neuropsychology, nursing, an epileptologist and neurosurgeon with a multidisciplinary discussion of all available therapeutic options. Such an evaluation would serve not only to assess candidacy for epilepsy surgery, but also to exclude alternative diagnoses masquerading as epilepsy such as non-epileptic seizures.

Patients considered for neuromodulation should have DRE and not be candidates for focal resection epilepsy surgery (e.g. seizure onset zone within eloquent cortex, more than one seizure focus, or patient does not wish not to pursue surgery).

Patients considering neuromodulation should be carefully counseled about relative effectiveness of neurostimulation techniques compared to other available medical and surgical treatment options as well as potential adverse events.

Neuromodulation should be undertaken only under the care of the multidisciplinary team and appropriately trained personnel. Patients should be followed up on a regular basis at either a regional epilepsy surgery center or a district epilepsy center comfortable with the care of such devices to adjust the device parameters, and monitor safety and efficacy.

5.1 Neuromodulation Techniques

5.1.1 Vagus Nerve Stimulator (VNS)

Stimulation is done through leads which are surgically implanted usually on the left vagus nerve in the neck, since stimulation of the right vagus nerve, which innervates the sino-atrial node, could cause bradycardia. After the carotid sheath is opened, two electrodes are wrapped around the vagus nerve and connected to a programmable pulse generator sitting sub-dermally on the upper part of the chest wall. The pulse generator then can be programmed wirelessly through a wand placed over the chest wall. The device has a magnet function, which is an external magnet, and is an optional stimulation that can be activated on demand. The patient or caregiver can use the magnet to abort seizures or minimize the severity of seizures when the patient is experiencing an aura or seizure warning. The magnet can be placed in the area where the stimulator is implanted, which will generate an additional stimulation.

Following the device implantation, it is turned on, with the stimulator programmed to deliver intermittent pulses of electrical stimulation lasting several seconds (usually between 7 and 30 seconds) at intervals of several minutes. Over the course of several weeks, the output current of the device is increased gradually, limited by the patient's ability to tolerate the sensation. A typical output current would be 1.5mA, but can range between 0.25 to 3.5 mA.

Other parameters include the frequency of the stimulation (between 20-50Hz, usually 30Hz), and the pulse width, usually 500μs. In addition to this continuous intermittent electrical stimulation, individual pulses of electrical stimulation can also be delivered on demand, signaled to the generator by passing a magnet over it. This is usually done by patients in response to their anticipation of a seizure by feeling an aura or seizure premonition. Newer models are also able to deliver stimulation in response to heart rate changes, as it has been shown that seizures are frequently associated with an increase in heart rate. Newer devices can also detect bradycardia and the position of the patient when the stimulation occurs (sitting or prone position), and the programming can be adapted to day and night parameters to adjust for the time of day when seizures are more frequent. Moreover, there is a function in the device that allows incremental changes to be made automatically every 1-3 weeks, reducing the need for frequent clinic visits.

The efficacy of VNS is supported by a limited number of randomized clinical trials. After initial pilot studies in an open label design, the first E03 blinded randomized group for VNS was performed at 17 sites in the US, Canada and Europe. Patients between 13 and 60 years old were enrolled and randomized to high (presumably therapeutic) pulse generator settings and to low (less or nontherapeutic) settings, with the hypothesis that the low stimulation might be ineffective, but would still be felt by patients, thus providing some degree of blinding. Initial published reports on the first 67 patients described a 31% mean seizure reduction in the high stimulation group compared to 11% in the low stimulation group (p=0.029), and 39% vs 19% of patients experiencing a 50% seizure reduction (p=0.0704) (The Vagus Nerve Stimulation Study Group, 1995). A follow-up study converting the initial 67 patients to the high stimulation paradigm for open label treatment up to 18 months showed 44% of patients with >50% seizure reduction. A later report on all 114 patients randomized into the trial showed 31% of patients had a >50% seizure reduction compared to 13% in the low group (p=0.02). A later E05 study randomized 198 patients to high and low stimulation as well, and showed a 27.9% vs 15.2% decreased in seizure frequency relative to baseline (p=0.02), and a significant difference in patients with 75% reduction in seizures, though statistical significance was not shown for difference in patients with 50% reduction in seizures.

Some studies have suggested that the efficacy of the VNS device may improve over longer periods of device implantation. Englot et al. (2016) report an increase in response rate over time, with the highest responder rates (60%) and seizure freedom rates (8%) seen >48 months post-implantation.

A 2015 Cochrane review of five RCTs concluded that VNS appears to be an effective treatment for people with drug-resistant partial epilepsy, as an add-on treatment. Results of the overall efficacy analysis show that VNS stimulation using the high stimulation paradigm was significantly better than low stimulation in reducing seizure frequency by 50% (Panebianco et al., 2015). There is a lack of high-quality evidence assessing the effectiveness of VNS in solely pediatric populations, although many of the previous trials included children.

Possible side effects associated with implantation and stimulation include voice alteration and hoarseness, cough, vocal cord paralysis, wire fracture necessitating electrode repair, throat pain, paresthesias, shortness of breath, nausea, headache, and superficial wound infections, without persistent serious side effects. The rate of Sudden Unexpected Death in Epilepsy (SUDEP) was calculated in a group of 791 patients with VNS for approximately 2 years each, for an incidence of SUDEP of 4.5 per 1000 person-years, a rate comparable to studies of young adults with intractable epilepsy not treated with VNS (Annegers et al., 1998). A study of 40,433 patients treated with VNS suggests a possible decrease in SUDEP risk during long-term follow-up (up to 10 years post-implantation), although no control group was included (Ryvlin et al. 2018).

The American Academy of Neurology Therapeutics and Technology Assessment Subcommittee reported in 1999 their opinion that there was sufficient evidence to consider VNS for epilepsy as effective and safe, and "indicated for adults and adolescents over 12 years of age with medically intractable partial seizures who are not candidates for potentially curative surgical resections such as lesionectomies or mesial temporal lobectomies".

In 2013 the American Academy of Neurology (AAN) published a guideline update on VNS based on a number of subsequent Class III studies, recommending that VNS may be considered for seizures in children, for Lennox-Gastaut Syndrome-associated seizures, and for improving mood in adults with epilepsy.

Following installation of the device, patients are often followed closely during the initial phase where the device parameters are adjusted to titrate to effect and tolerability. Most typically, the output current is adjusted while the patient is otherwise kept on a standard paradigm of a stimulator on time of 30 seconds and off time of 5 minutes, with 30Hz stimulation and pulse width of 500 μs. Other stimulation paradigms have been tried such as rapid cycling, which usually entails 7 seconds on and 30 seconds off stimulation. Such paradigms have not been conclusively shown to be better than the standard stimulation paradigm, although some authors have found that a later switch to rapid stimulation in non-responders can be associated with improvement in some patients. The parameters used need to be adjusted to each patient, minimizing side effects and maximizing tolerability.

Recommendations (Morris et al., 2013):

- VNS may be considered as adjunctive treatment for children and adults with focal or generalized epilepsy.
- Children and adults should be carefully monitored for site infection after VNS implantation.
- VNS may be considered in patients with Lennox-Gastaut syndrome.
- VNS is possibly effective for mood improvement in adults and children with epilepsy.
- VNS may be considered progressively more effective in patients over multiple years of exposure.
- Optimal VNS settings are still unknown, and the evidence is insufficient to support a recommendation for the use of standard stimulation vs rapid stimulation to reduce seizure occurrence.
- Close monitoring of patients implanted with VNS and adjustment of parameters according to tolerability are recommended.

5.1.2 Deep Brain Stimulation (DBS)

There is one multicenter randomized controlled clinical trial known as the SANTE (Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy) trial, showing evidence for safety and efficacy in epilepsy of DBS at the anterior nucleus of the thalamus (Fisher et al., 2010). The anterior nucleus of the thalamus is part of the circuit of Papez, which involves connections from the hippocampus, fornix, mammillary body, anterior nucleus of the thalamus and the cingulate gyrus, feeding back into the hippocampal formation. Electrical stimulation at the anterior nucleus of the thalamus theoretically inhibits this nucleus, but the mechanism by which DBS at this site exerts its effect is likely more complicated than simply impeding propagation of seizures through this network by inhibiting one part of the circuit, and is poorly understood.

Bilateral stereotactic placement of multicontact electrodes in the anterior nucleus of the thalamus is performed usually under general anaesthesia using a frame or frameless system. MRI can be performed beforehand to accurately identify the target site. After the leads are placed, the right and left side connectors are tunneled subcutaneously to the dual-channel pulse generator located subcutaneously on the chest wall. Intra-operative fluoroscopy or post-operative MRI is used to confirm correct placement of the leads. When the device is turned on, it is usually programmed to deliver stimulation at a voltage of 5 volts, with 90us pulses at 145Hz, on for 1 minute and off for 5 minutes. Parameters can be changed, including increases in output voltage up to 7.5V or stimulation frequency to 185Hz.

The SANTE study was conducted in 110 patients who were treated with a 3 month blinded phase in which half received active treatment and half received no stimulation. Following this phase, all patients were unblinded and received active treatment. During the blinded phase, the stimulated group showed greater improvements in seizure frequency compared to the control group over each of the 3 months of follow-up such that by the end of the blinded phase, the stimulated group had a 40.4% reduction in seizure frequency compared to 14.5% in the control group.

In the unblinded phase of the trial, the 50% responder rate was 43% at 13 months, 54% at 25 months and 67% at 37 months. The study investigators did note that subjects with temporal lobe origin seizures had greater benefit from stimulation in the blinded phase compared to those with extra-temporal or multifocal epilepsy.

Adverse events reported in the study included depression in 14.8% of active treatment arm compared to 1.8% of controls, memory impairment in 13% of active treatment arm compared to 1.8% of controls, paresthesias in 18.2% of participants, and implant site infections in 9% of patients. 16.4% of patients withdrew from the study due to adverse events. Asymptomatic hemorrhage was observed in 4.5% of patients. Death was observed in 5 patients (4.5%), one in the baseline phase before surgery attributed to SUDEP, none during the double-blind phase, one due to drowning in a bathtub, one due to suicide, and two more due to SUDEP in long-term follow-up. None of these deaths was judged to be device-related.

DBS at the centromedian nucleus of the thalamus has been studied in a number of case series and a single controlled trial. An initial pilot study in 1987 involving five patients with primary generalized or multifocal epilepsy described a 60-100% improvement in complex partial seizures and an 80-100% improvement in generalized tonic-clonic seizures (Velasco et al., 1987). This report was followed in 1993 by a larger series of 23 patients from the same group who observed a good response to stimulation in 12 patients whom they divided into either patients with generalized tonic-clonic seizures (9), or epilepsia partialis continua (3), but a poor response in the remaining 11 patients who had either complex partial seizures (5) or tonic seizures (6) (Velasco et al., 1993). This group reported in 2001 that they had followed 49 patients over the course of between 6 months and 15 years for centromedian nucleus of the thalamus stimulation, and reported efficacy for generalized tonic-clonic seizures, tonic seizures, and atypical absence seizures, but not complex partial seizures (Velasco et al., 2001).

Notably, the single controlled pilot trial of centromedian stimulation for epilepsy published in 1992, using a double-blind cross over protocol with 3 months blocks and a 3 month wash-out period, did not show any efficacy for centromedian nucleus stimulation (Fisher et al., 1992). However, it was too small to evaluate efficacy of centromedian stimulation, having only seven patients, and using lower stimulation voltages than Velasco et al.

A 2021 follow-up study of patients in the SANTE trial showed a median seizure reduction of 75% after 7 years of treatment, though the retention rate of participants at 7 years was only 66% (Salanova et al., 2021). Depression was observed in 37.3% of participants, and 30% reported memory impairments. The rate of SUDEP was 2.0 deaths for 1000 person-years, which is below the rate of 6.3-9.3 per 1000 person-years in patients with drug-resistant epilepsy (Devinsky et al. 2016).

A 2017 Cochrane review of twelve RCTs concluded that a significant reduction in seizure frequency was found for anterior thalamic DBS (high-quality evidence), responsive ictal onset zone stimulation (high-quality evidence) and hippocampal DBS (moderate-quality evidence). No statistically significant effects could be demonstrated for centromedian thalamic DBS, nucleus accumbens DBS or cerebellar stimulation; however, the evidence was rated as low to very low quality (Sprengers et al., 2017).

Reported adverse events included postoperative asymptomatic intracranial hemorrhage in 1.6% to 3.7% of patients and postoperative soft tissue infections in 2.0% to 4.5% of patients in the two largest trials. Despite the reduction in seizure frequency seen with anterior thalamic DBS and responsive ictal onset zone stimulation, there was no clinically meaningful impact on quality of life, and anterior thalamic DBS was associated with higher rates of self-reported depression and subjective memory impairment. Although seizure reductions have been reported with both centromedian and anterior thalamic DBS in children (Yan et al., 2018), to date there have been no RCTs investigating the use of DBS in pediatric epilepsy patients.

A recent RCT of DBS for Lennox-Gastaut syndrome found that 50% of patients who received DBS to the centromedian thalamic nucleus had a ≥50% seizure reduction, compared with 22% of controls.

Although this difference was not statistically significant, there was a significant reduction in electrographic seizures in the stimulation group measured objectively from intermittent 24-hour ambulatory EEGs, suggesting a therapeutic benefit (Dalic et al., 2022).

5.1.3 Responsive Neurostimulation

The ability to abort seizures through application of a current directly to the cortex has been known for years, both in animal models, as well as in humans undergoing electrocorticography. While DBS and VNS systems deliver their programmed impulses at regular intervals with the intent to prevent seizures, responsive neurostimulation continuously monitors EEG with chronically implanted depth and/or subdural strip electrodes, and only delivers an electrical stimulus when a seizure has been detected.

The first device with such capabilities underwent randomized clinical trials which were reported in 2011 (Morrell 2011). Two hundred and forty subjects experiencing three or more disabling focal seizures per month were enrolled, of which 191 were implanted. After a 3-month pre-treatment baseline, patients were implanted with the device; then after a 4-week perioperative phase, patients underwent a 12 week blinded period in which 97 subjects received active treatment, and 94 subjects received sham treatment. Both groups experienced an initial reduction in seizures after electrode implantation, but a reduction in mean seizure frequency could still be demonstrated in the treatment compared to sham group during the blinded phase (-37.9% n=97 vs -17.3% n=94, p=0.012).

Serious adverse events (SAEs) occurred in 2.5% of the 191 subjects enrolled in the trial. SAEs in the first month included site infection (5 patients) requiring explant of the device in one patient, intracranial hemorrhage in 4 patients, 3 of whom required surgical intervention, as well as transient apraxia and dysphemia in one patient, and a procedure to revise the location of the leads in one patient. In longer term follow-up, SAEs included increased frequency of seizures in one patient and need for surgical revision of implanted leads to improve lead location, or repair damaged leads. Six subjects died during the study, four due to possible or definite SUDEP (one being in the sham group without stimulation enabled), one due to lymphoma, and one due to suicide.

There have been three open-label extension studies reporting follow-up outcomes from the same population (Heck et al., 2014; Bergey et al. 2015; Nair et al., 2020). The median percent seizure reduction was 53%, 66%, and 75% at 2, 5, and 9 years of follow- up, respectively. Similarly, responder rates were 55%, 59%, and 73% at 2, 5 and 9 years, respectively. At 9 years, 18.4% of patients (47 of 256) had experienced ≥1 year of seizure freedom, with an average seizure-free period of 3.2 years. A significant improvement in quality of life was seen after one year and maintained through year 9 of treatment (Nair et al., 2020). There were no SAEs related to stimulation, and the SUDEP rate of 2.0/1000 patient stimulation years is favorable for other treatment-resistant epilepsy groups (Devinsky et al., 2018).

RNS is approved for use in the United States, but is not currently approved in Canada.

5.1.4 Hippocampal stimulation

Electrical stimulation of the hippocampus as a possible treatment for DRE has been studied by several groups. In a Canadian study, four patients with mesial temporal lobe epilepsy (MTLE) underwent implantation of a chronic stimulating depth electrode along the axis of the left hippocampus (Tellez-Zenteno et al. 2006). This study used continuous, subthreshold electrical stimulation (90 microsec, 190 Hz) and a double blind, multiple cross-over, randomized controlled design, consisting of three treatment pairs, each containing two 1-month treatment periods. During each treatment pair the stimulator was randomly turned ON 1 month and OFF 1 month. Hippocampal stimulation produced a median reduction in seizures of 15% and 3 patient's seizures improved; however, the results did not reach significance. Effects seemed to carry over into the OFF period. This study demonstrated possible benefits and absence of adverse effects of hippocampal electrical stimulation. However, the effect sizes observed were smaller than those reported in non-randomized, unblinded studies.

The effect of continuous electrical stimulation of the hippocampus bilaterally on seizures and memory was assessed in two subjects with seizures from both mesial temporal lobes in another Canadian study (McLachlan et al., 2010). A double -blind, randomized, controlled, cross-over trial design was utilized. Two electrodes with four contacts each were implanted along the axis of the hippocampus bilaterally. Simultaneous stimulation of all electrodes contacts was either on or off during each 3-month interval. Seizure frequency decreased by 33% in both patients during stimulation and remained lower by 25% for the 3 months after stimulation was turned off before returning to baseline ($p<0.01$). No consistent change in objective or subjective measures of memory occurred. A 2017 Cochrane review suggests that compared to sham stimulation, hippocampal DBS may moderately reduce seizure frequency in patients with drug-resistant epilepsy; however, the limited number of patients preclude firm statements on safety and tolerability of hippocampal DBS (Sprengers et al., 2017).

5.1.5 Transcranial Magnetic Stimulation (TMS)

Transcranial Magnetic Stimulation (TMS) is a non-invasive brain stimulation technique which has been shown to suppress cerebral cortical hyperexcitability. A number of open-label and controlled studies in patients with various forms of focally originating DRE have shown its potential benefits but different methods of stimulation have been used. Repetitive TMS (rTMS) was no better than placebo for seizure reduction among 43 persons with DRE in a randomized, double-blind, sham-controlled, cross over multicentre Italian study (Cantello et al., 2007). Paired-pulse TMS (ppTMS) has been of limited effectiveness so far as well.

A recent systematic review of eight RCTs investigating the use of TMS in patients with DRE concluded that although rTMS appears to be safe, evidence for its effectiveness at reducing seizures is lacking (Walton et al., 2021). In addition, a high degree of methodological variability across studies was reported. Until large scale studies validate the role of TMS in epilepsy, it cannot be recommended as a routine clinical tool.

5.1.6 External Trigeminal Nerve Stimulation (eTNS)

The safety and efficacy of External Trigeminal Nerve Stimulation (eTNS) in patients with DRE was studied in one class II double-blind randomized controlled trial design in 50 persons with epilepsy over 18 weeks (DeGiorgio et al., 2013). Although there was improvement within the active treatment group alone, there was no significant difference in effect between the treatment and control groups. However, a recent RCT of 40 patients provided Class II evidence that eTNS reduces seizure frequency in patients with focal drug-resistant epilepsy (Gil-Lopez et al., 2020). Additional studies with larger numbers of participants and longer follow-up periods (> 1 year) are required to determine the potential utility of eTNS as a treatment option.

5.1.7 Transcutaneous Auricular Vagus Nerve Stimulation (ta-VNS)

Transcutaneous auricular vagus nerve stimulation (ta-VNS) is a non-invasive therapy that targets the auricular branch of the vagus nerve. The mode of action is not fully understood, but stimulation may stabilize large-scale epileptic network activity (von Wrede et al., 2021).

The safety and efficacy of bilateral ta-VNS for the treatment of paediatric epilepsy was studied in 14 patients with DRE over 24 weeks with stimulation of the auricular concha using an ear vagus nerve stimulator (He et al., 2013). The responder rate was 53.85% from week 17 to the end of week 24 in 13/14 subjects. A randomized, double-blind clinical trial of 58 adults with DRE found that 20 weeks of ta-VNS was well-tolerated and reduced seizure frequency by 34%; however, there was no significant difference between active (25 Hz) and sham (1 Hz) stimulation (Bauer et al., 2016).

More recent studies have suggested ta-VNS may be an effective adjuvant treatment for drug-resistant epilepsy; however, there is insufficient evidence to make treatment recommendations at present.

6. Non-Pharmacologic Management of Epilepsy

5.1 Vitamins

Currently there is no evidence to support that folic acid, thiamine, Vitamin D or Vitamin E improve seizure control or prevent side effects in people with epilepsy. Further studies are needed. Vitamin D supplementation appears to have a positive effect on bone turnover markers, particularly alkaline phosphatase, in adults with epilepsy, but more trials are needed to clarify the effect of vitamin D supplementation on bone health. Vitamin D is also highly recommended in patients taking enzyme-inducing ASMs to minimize the risk of osteoporosis. Folic acid supplementation (0.4 - 4 mg/day) is highly recommended in women of childbearing age to minimize the teratogenic risk associated with certain ASMs and unplanned pregnancies; however, due to the weak evidence in the literature, the optimal dose of folic acid is still a question.

5.2 Yoga and mindfulness

Currently there is no evidence to support the efficacy of yoga as a treatment in the management of DRE. However, techniques such as cognitive behavioural therapy, yoga or mindfulness-based interventions that focus on thought restructuring can be beneficial for stress reduction in people with epilepsy. There is moderate-quality evidence that psychological and self-management interventions are beneficial for adults and adolescents with epilepsy, by improving overall quality of life and emotional well-being and reducing fatigue (Michaelis, 2017).

5.3 Melatonin

It is not possible to draw any conclusion about the role of melatonin in reducing seizure frequency or improving quality of life in people with epilepsy. Currently there is no evidence to support the use of melatonin as add-on therapy for the treatment of epilepsy.

5.4 Exercise and sports

Currently there is no evidence indicating that exercise is effective in treating epilepsy. However, regular exercise can improve cognitive function at all ages, and enforcing a sedentary lifestyle can have deleterious effects and impact on psychosocial development, independence, and mental health. Engaging in physical exercise and sport activities has positive medical and psychosocial effects for people with epilepsy, including increased self-esteem, socialization, and improvement in long-term general health.

Determining whether a patient can participate in specific physical activities or sports requires careful clinical assessment of the individual risk–benefit ratio, particularly with respect to the risk of a seizure occurring during the activity and related implications, and is a responsibility to be shared among physicians, patients and parents if the person with epilepsy is a child or adolescent (Capovilla et al., 2016).

5.5 Herbal treatments

There is pre-clinical evidence for use of some herbal medication such as kava (Piper methysticum) and mistletoe (Viscum sp) but no clinical evidence to support their use.

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Appendix 1: Guideline on managing excess ketosis, metabolic acidosis, and hypoglycemia in diet therapy

a) Managing excess ketosis and acidosis

- Each institution may have its own protocol for managing excess ketosis.

- Excess ketosis can manifest in the context of recent diet therapy initiation which requires further fine tuning, or during illness.

- Common symptoms of severe acidosis include: nausea, vomiting, lethargy and Kussmaul breathing. Acidosis can be enhanced when carbonic anhydrase inhibitor medications are also concurrently being administered with the diet therapy.
  - Excess ketosis must be managed immediately with the administration of carbohydrates.
  - Immediately treat with 15 mL or orange juice or 10 mL or apple juice and recheck urine ketones
  - If symptoms of excess ketosis do not improve 15-20 minutes after juice was administered, repeat treatment with juice
  - If ketone levels are persistently elevated and the child is symptomatic, contact the dietitian as a diet change may be indicated
  - 2.5% or 5% dextrose/saline IV solution may be administered in children who are unable to tolerate oral fluids due to excessive vomiting. Hospitalization will be required for these children including further evaluation and investigation. Laboratory investigations should include urea, creatinine, electrolytes, glucose, capillary blood gases and infection screen as indicated upon further clinical evaluation

- Ensuring all fluid requirements (particularly the water) are being provided or consumed helps minimize acidosis.
  - Consider increasing the water intake by 100-200 ml to help manage acidosis.
  - The strength of the diet can also be reduced so as to include more carbohydrates and less fat.
  - If acidosis occurs under acute circumstances bicarbonate can be given orally or IV to support correction (Kossoff et al. 2009).
  - Adjusting the carbonic anhydrase inhibitor medications may also need to be considered.

b) Managing Symptomatic Hypoglycemia

- Each institution may have a different method of identifying and managing hypoglycemia in children on the diet. Correction of hypoglycemia usually requires the use of a small volume of juice (20-30 ml) and closer monitoring.

- Contact the dietitian in the team for assistance in managing.

Appendix 2: Managing intercurrent illness with diet therapy

When Vomiting Occurs

- Treat vomiting with dimenhydrinate suppositories.
- Discontinue giving the specific prescribed diet (foods or formula).
- Use diluted electrolyte solution (paediatric rehydration solution) calculated based on patient's need.
- Measure urine ketones with every void and blood glucose every 4-6 hours.
- Once vomiting has stopped, gradually reintroduce either the appropriate diet foods or formula.
- Contact the RD for guidance.

Appendix 3: NPO Guidelines for diet therapy (following is just an example of management)

- In situations where a child on diet therapy requires a procedure for which they must be NPO, request that the procedure be done as early as possible to minimize the time required for the child to be NPO.

- Use IV normal saline for maintenance fluids.

- No IV dextrose solutions unless absolutely indicated. If required, use ½ or ¼ strength.

- Check blood glucose every 6 hours.
-
- If blood glucose is < 2.5 mmol/L or if symptomatic for hypoglycemia, treat immediately with 50 mL D5W and recheck blood glucose in 1 hour.

- If blood glucose is 2.5 – 3.0 mmol/L, treat with 25 mL D5W.

- Check urine ketones with each void.

- If urine ketones are > 16 mmol/L and symptomatic, treat with 25 mL D5W.

- If urine ketones are between 8 mmol/L and 16 mmol/L and symptomatic, treat with 12.5 mL D5W.

Appendix 4: Children on diet therapy for epilepsy who require surgery

- Communicate with the surgeon and anaesthetist to learn the length of time required for the child's surgical procedure.
- Each institution may have its own specific surgical protocol for children on the diet therapy who will undergo surgery.
- Provide written therapeutic diet management guidelines to the same day admission unit, anaesthetist, surgeon, recovery room and unit to which the child will return to ensure that the child remains in ketosis before, during and after surgery.
- Ask the anaesthetist and/or surgeon to maintain normoglycemia during the surgical procedure.
- Prolonged surgical procedures increase the risk for developing metabolic acidosis. Check serum pH or bicarbonate levels to monitor for acidosis. Check these levels every 2-3 hours during surgical procedures that last longer than 3 hours.
- Monitor blood pH levels and/or bicarbonate levels in the postoperative period until the child is on the full therapeutic diet.

Appendix 5: Information to patients and families regarding diet therapy

Patients and families should receive written information about the different types of diet therapies for epilepsy, side effects and complications of diet therapy. Educational materials should discuss contraindications, process of diet initiation and ongoing maintenance and monitoring, admission to hospital, members of the diet therapy team, supplies required including cost, financial considerations, sources of financial assistance, and additional resources available. This should be provided to patients and families either prior to the clinic consultation visit, or at the visit. Specific hospitals may have their own written materials regarding diet therapy services.

Conducting information sessions is an effective way to allow patients and families to hear information about the types of diets, ask questions of the diet therapy team members, and to receive peer-to-peer support. These sessions can be instrumental in providing excellent information to help patients and caregivers make more informed decisions.

Other sources of information about diet therapy include:

London Health Sciences Centres: The Ketogenic Diet
https://www.lhsc.on.ca/paediatric-epilepsy-program/the-ketogenic-diet

Charlie Foundation for Ketogenic Therapies
https://charliefoundation.org/

Matthew's Friends
https://www.matthewsfriends.org/

Appendix 6: Diet Therapy Team

The multidisciplinary team should include epileptologist(s), registered dietitian(s), nurse(s) and social worker(s) within a comprehensive epilepsy program. If resources are available, services of a child life specialist, nurse practitioner and pharmacist are encouraged.

Role and Responsibilities:

1. Epileptologist

- Provide leadership to the multidisciplinary team of health professionals in the diet therapy team and is responsible for the quality of care delivered.
- Determine medical suitability of patients with epilepsy for diet therapy, and the type of diet in discussion with the dietitian.
- Oversee and participate in the clinical management of patients from initial consultation to the diet therapy service through to discharge and transition to adult care, and shall be the most responsible clinician (MRC) or physician (MRP) for the patient.
- Oversee the management of complications of the diet.
- Determine the macronutrient distribution goal for each patient in collaboration with the dietitian.

2. Registered Dietitian

a) Pre-diet assessment:
- Refer to section 7b

b) Initiating the diet:
- Determine the diet plan for patients as per the diet prescription.
- Educate the caregivers to safely manage the diet at home including managing the diet during times of illness (can be done by nurse practitioner too).
- Review monitoring expectations that need to be performed: e.g. ketones, blood glucose, weight, height/length (can also be done by nurse or nurse practitioner).
- Monitor for complications (e.g. hypoglycemia, severe ketoacidosis, vomiting, diarrhea, poor intake).
- Modify the diet if necessary, based on pre-set goals of therapy in discussion with the MRP.
- Complete the nutrition assessment to determine the supplemented micronutrient requirements.
- Coordinate with physicians/nurse practitioners and family pharmacies to ensure sufficient diet formulas/products are ready at time of discharge, in cases of inpatient initiation.

c) Fine-tuning and Follow-up:

- Provide support to the families via phone or email (can also be done by RN/NP).
- Complete frequent full nutritional assessments.
- Make adjustments to the micronutrient supplements.
- Implement adjustments to diet as needed in discussion with the MRP.

3. Nurses

a) Ambulatory Setting:

- Medication reconciliation.
- Provision of preliminary information about the diet therapy in epilepsy, be it written information or in the form of teaching during an information session.
- Obtaining vital signs, height, weight, head circumference.
- Obtain initial or interval history including seizures.
- Providing instructions on obtaining fasting blood work and urine testing for follow-up visits as needed.

Appendix 6: Diet Therapy Team

- Provision of telephone triage and support when issues arise (e.g. child experiencing complications).
- Participation in the diet therapy information sessions.
- Assists in connecting families for peer-to-peer support.

b) In-Patient Setting:

- Orientation to the inpatient unit.
- Nursing assessment.
- Obtaining vital signs, height, weight, head circumference.
- Medication reconciliation.
- Review of blood work results (if done on morning of diet initiation).
- Teach/review with parents how to use the commercial glucometer and review parameters for hypoglycemia.
- Teach/review how to measure urine ketones using prescribed strips.
- Teach parents how to measure urine specific gravity.
- Monitor for side effects of the diet during initiation.
- Monitor for complications of the diet including vomiting, diarrhea, hypoglycemia, hyperketosis, acidosis.
- Monitor parental progress with diet initiation.
- Monitor child's reaction to the diet and watch for signs of food refusal.
- Ensure all medications from pharmacy are in tablet form and not liquid form with certain exceptions that have been reviewed by the epileptologist, pharmacist, and dietitians and approved for use.
- Monitor and record all seizures.
- Communicate any complications and management issues to the physician/nurse practitioner and RD.
- Reinforce how to manage hyperketosis, hypoglycemia, dehydration.
- Monitor for constipation (if on therapeutic diet) or diarrhea (if on MCT oil).
- Ensure all medications are in tablet form with the exception of those liquid forms approved (e.g. specially formulated omeprazole), and that IVs do not contain dextrose (unless clinically indicated) including pre-mixed IV antibiotics.
- Monitor blood glucose and ketones.

4. Social Worker

- Work collaboratively with the members of the multidisciplinary team to understand the patient and family's social and emotional needs and how they impact the patient's medical condition and attitude toward treatment (e.g. food refusal, force-feeding).
- Work with patients and families to understand their beliefs about the illness.
- Work as a resource to the interdisciplinary team in responding to challenges.
- Work as a resource to the interdisciplinary team in helping them to respond to challenging patient and family situations.
- Provide support to patients and families when required to help manage feelings of anxiety regarding dietary treatment to facilitate adherence to diet treatment.
- Work with the members of the team in order to assist the patient in understanding the complexity of epilepsy and diet treatment.
- Address patient and family needs as they relate to resources, funding and advocacy.
- Provide individual, couple and family therapy as needed to support the wellbeing of the patient.
- Assist with the transition from paediatric to adult epilepsy care.
- Refer to community agencies and community-based support services as needed.
- Participate in group teaching/information sessions.

Appendix 6: Diet Therapy Team

- Work with schools to help teachers and support workers understand the diet therapy and the importance of supporting successful adherence in the school setting and acceptance among peers.

5. Child Life Specialist

- Assess the physical, social and emotional responses of the child and family to the diet therapy for epilepsy.
- Enhance patient coping by utilizing therapeutic play interventions.
- Assist the child in preparing for the diet by utilizing creative meals and developing self-mastery.
- Advocate for the psychosocial needs of patients and families.

6. Nurse Practitioner

- Screening of referrals to the 'diet therapy for epilepsy' service.
- Initial patient clinical consultation including completing a comprehensive medical history, seizure history, clinical course and treatment of seizures, medication history, review of current medications, physical examination.
- Assessment of potential complicating factors such as poor food or fluid intake, failure to thrive, constipation, gastroesophageal reflux, chronic metabolic acidosis, renal calculi.
- Ordering of laboratory tests and appropriate diagnostic studies to further assess potential complication factors such as a feeding study, consultation for gastrostomy tube.
- Review of medical record to ensure there are no contraindications to the diet such as metabolic disorders.
- Adjustment of liquid medications to tablet form in preparation for the diet.
- Assess developmental and psychosocial history and potential psychosocial barriers to the diet.

7. Pharmacist

- Provide guidance regarding carbohydrate content of medications and supplements.
- Advise on effect of diet on efficacy of medication (e.g. high fat diet, decreased absorption of medication).

Appendix 7: Diet therapy procedures

1. Pre-Diet Assessment

a) Referral & Screening

Diet therapy for epilepsy should be undertaken only after thorough clinical evaluation of the patient. In most situations, diet therapy is offered to patients with drug-resistant epilepsy. It is essential to establish a correct epilepsy diagnosis and ensure appropriate medical therapies have been tried before considering diet therapy. Patients who are potential surgical candidates should have appropriate work up to decide whether they are in fact surgical candidates, as surgical treatment may provide a more definitive epilepsy treatment than diet therapy. Therefore, it is essential that all patients who are being considered for diet therapy be first evaluated by an epileptologist. Evaluation may include video EEG monitoring to capture the clinical events/seizures.

b) Pre-initiation Diet Assessment

The pre-initiation diet assessment should include the following:

- Anthropometrics (height, weight, IBW)
- Nutritional Intake
- Nutrition-focused Clinical Assessment
- Biochemical indexes
- Social Determinants of Health
- Determination of food allergies
- Cultural or religions preferences that require accommodation

The information gathered from the assessment will assist in determining the type of diet therapy required, need for possible commercial dietary products, estimate of financial burden, method of diet initiation and potential complications during diet therapy.

Prior to diet initiation, it is crucial to discuss the psychosocial issues that may affect its implementation. Such topics include the critical role of caregivers in administering KDT, time requirements related to meal preparation, cost of food, additional supplementation (including pill burden and method of delivery), and side effects. Any behavioural or personality traits in the child or parent that may influence the administration of the diet should be identified (Kossoff et al., 2018).

c) Baseline Laboratory and Diagnostic Testing

The International Ketogenic Diet Study Group recommends the following (Kossoff et al., 2018):

- Complete blood count with platelets
- Electrolytes to include serum bicarbonate, total protein, calcium, zinc, selenium, magnesium, and phosphate
- Serum liver and kidney tests (including albumin, AST, ALT, blood urea nitrogen, creatinine)
- Fasting lipid profile
- Serum acylcarnitine profile
- Vitamin D level
- Urinalysis
- Urine calcium and creatinine
- Anticonvulsant drug levels (if applicable)
- Urine organic acids
- Serum amino acids
- EKG (routine practice in Ontario centers to ensure QT interval is normal)
- Ancillary testing (optional)
  - Renal ultrasound and nephrology consultation (if a history of kidney stones)
  - EEG
  - Brain MRI
  - Cerebrospinal fluid (CSF) (if no clear etiology of seizures/epilepsy has been identified)
  - Team to decide on other tests depending on co-morbid conditions, and use of drugs including ASMs

Appendix 7: Diet therapy procedures

d) Feeding Assessment

If during the initial assessment there is concern of aspiration, a feeding assessment and a video fluoroscopy should be ordered to rule out risk of aspiration. Children who are found to aspirate on further investigation should be offered the option of receiving the diet via enteral feeding tube.

When assessing a child to determine candidacy for the diet therapy, they should be assessed for the following symptoms when eating and drinking:

- Vomiting
- Eating and gagging on textures
- Eating a limited variety of food/selective
- Slow weight gain
- Refusal to eat
- Limited volume/not eating enough
- Difficulty swallowing
- Refusal to swallow/holding of food in mouth
- Difficulty progressing to table food

e) Financial Assessment

It is important to provide information about the cost of the prescribed diet to patients and families. The exact costs will be determined at the time of diet initiation depending on how the patient tolerates the diet, and on their individual micronutrient needs. Families should be encouraged to review the costs and determine whether their insurance will cover some of the costs or whether they require financial assistance. The social worker can help families navigate through the various funding sources.

Other associated costs include food storage supplies, artificial sweeteners, artificial flavorings, carbohydrate free creams, lotions, toothpaste, and cost of parking for follow-up visits to the hospital.

f) Child Life Assessment

The Child Life Specialist may meet with the child and family prior to commencing a diet. By utilizing age appropriate methods, the Child Life Specialist assists with the transition to the new diet and encourages children to actively participate in activities to support diet initiation.

g) Diet Initiation Planning

All medications are to be assessed for carbohydrate content. Liquid suspensions should be converted to tablet form, if possible. For some children who are unable to swallow tablets, compounded preparations may be created using certain sweeteners. The compounding pharmacist should consult with the dietitian to determine the carbohydrate content of the medication and proposed liquid vehicle in which the medication is to be formulated to see if it can be incorporated into the diet. Prescriptions for diet testing supplies should also be provided to patients and their families. Parents are instructed to order a decimal gram scale and bring it with them on admission so that the scale can be calibrated and it can be used during the diet initiation admission so parents become familiar with using the scale.

A letter that summarizes the diet therapy should also be provided to patients and caregivers. The letter should summarize the purpose of the diet therapy and that it is being monitored by the diet team. Suggestions on management (eg. avoid liquid medications, dextrose containing IVs fluids including IV antibiotics premixed in dextrose, and IVIG with high dextrose content) along with suggested monitoring can also be included.

Appendix 7: Diet therapy procedures

Parents are instructed to present this letter to health care providers that may become involved with their child's care (e.g. EMS, emergency room staff, pharmacist, dentist, home care staff).

h) Setting the Goals

The multidisciplinary team and the patients (and or caregivers) should discuss the goals of diet therapy. Practical goals with respect to seizure control, change/reduction in antiseizure drugs, and in the case of epileptic encephalopathy, the desired neurocognitive outcome or sleep EEG parameters (in encephalopathy associated with electrical status epilepticus of sleep) should be set. An appropriate response to seizure recurrence might include change in ASMs, fine tuning the diet or both. This goal should be set, if possible, at the time of diet initiation.

2. Follow Up Guidelines

a) Follow Up Visits

Frequency of follow-up with the epileptologist, dietitian, and other members of the multidisciplinary team (if applicable) should be decided by the multidisciplinary team. Currently, most centres recommend children on classic KDT be seen at 1, 3, 6, 9, and 12 months in the first year, with visits spaced to every 6 months after that (Kossoff et al., 2018). If clinically indicated, children less than 1 year of age should be evaluated more frequently as should those with growth, feeding issues, or nutritional deficiencies. A nutritional assessment and medical evaluation of the diet, including growth, appropriateness of prescription, compliance, supplementation and side effects should be conducted.
Ongoing contact with children and families between the dietitian and nurses should be maintained for fine-tuning/maintenance of the diet between visits and for any troubleshooting. Any change in the pre-set goals should be approved by the most responsible provider.

b) Investigations

The International Ketogenic Diet Study Group recommends the following laboratory diagnostic tests during follow-up (Kossoff et al. 2018):

- Complete blood count with platelets
- Electrolytes to include serum bicarbonate, total protein, calcium, magnesium, and phosphate
- Serum liver and kidney profile (including albumin, AST, ALT, blood urea nitrogen, creatinine)
- Vitamin D level
- Fasting lipid profile
- Free and total carnitine
- Urinalysis
- Selenium level
- Anticonvulsant drug levels (if applicable)
- EEG (at KDT discontinuation consideration)
- Optional investigations include:
  - Serum β-hydroxybutyrate (BOH) level
  - Urine calcium and creatinine
  - Zinc and copper levels
  - Renal ultrasound
  - ECG
  - Bone mineral density (DEXA) scan after 2 years on the KD
  - Team to decide on other tests depending on co-morbid conditions, type diet used, and use of drugs including antiepileptic drugs

Urine or serum ketones should be checked at home by parents several times per week, preferably at different times of the day (Kossoff et al., 2018). As part of their diet therapy training, parents should be taught to be prepared in the event of an emergency.

Appendix 7: Diet therapy procedures

In the event of an emergency, parents should bring a letter from the diet therapy team indicating that they are on a diet and that their child may not have oral liquid medications, IV dextrose solution (only if clinically indicated).

Parents should be instructed to bring in their child's most recent diet recipe should an admission to hospital be required. This will allow for the Diet Office to be able to prepare the appropriate diet. After business hours, if parents anticipate that they may need to take their child to the Emergency Department, they should, if time permits, prepare some diet shakes to bring with them or meals in the event that the Diet Office is closed or there is a delay in getting the specific diet. Parents should be encouraged to bring their glucometer, strips for checking ketones, and lancets to hospital in the event that an admission is required during emergency situations.

Diet therapy order sets should be created if computerized orders are generated for patient care delivery. This will allow consistency in patient orders and for other treating teams (e.g. paediatrics) to ensure appropriate orders are entered and that the diet is adhered to should a child be admitted off service.

c) Weaning the Diet

The timing and actual method of discontinuation of diet therapy for epilepsy is often individualized based on the patient's response to the diet (Kossoff et al. 2009). The International Ketogenic Diet Study Group suggests consideration should be given to discontinue diet therapy for epilepsy after 3 months if unsuccessful, and 2 years in children with >50% seizure reduction; however, longer diet durations are necessary for GLUT-1 and PDHD and may be appropriate based on individual responses for intractable epilepsy (Kossoff et al. 2018). Conversely, shorter durations may be appropriate for patients with infantile spasms and status epilepticus. For children in whom seizure control is >90% and adverse effects are minimal, KDTs may be continued for several years. Diet therapy for epilepsy works rapidly when effective, with 75% of children responding within 14 days (Kossoff et al. 2008). Therefore shorter diet therapy durations may be adequate to assess efficacy. Should seizures worsen for more than a few days after starting diet therapy, similar to ASMs, it can be discontinued immediately.

During discontinuation, a gradual wean over 1–3 months is recommended, and during this time period, nutritional supplementation needs to be continued. If seizures worsen, the KD can be increased to the previously effective formulation (Kossoff et al. 2018). For patients in whom the classic KD proves useful and necessary long-term, it may be reasonable to consider changing to the MAD or LGIT after several years.

d) Transition to Adult Care

Data on transition to adult service from paediatric service in diet therapy for epilepsy is limited. For the majority of adults with epilepsy, anti-seizure management is not vastly different between paediatric and adult providers. However, continuation of diet therapy as an adult requires the services of a trained adult neurologist familiar with either the KD or MAD, and an adult dietitian as well. Although paediatric KD teams can continue to provide care, intermittent hospitalizations to adult units and issues such as pregnancy, living independently, and different nutritional requirements make this potentially problematic for adults (Kossoff et al. 2013). Based on a small series of patients, some authors have suggested that individual hospitals and paediatric neurology clinics can make their own personal decisions on how best to handle transitioning these patients; however, the authors believed that having an adult epilepsy diet center is ideal (Kossoff et al. 2013).

Appendix 8: Obtaining cannabis for medical use

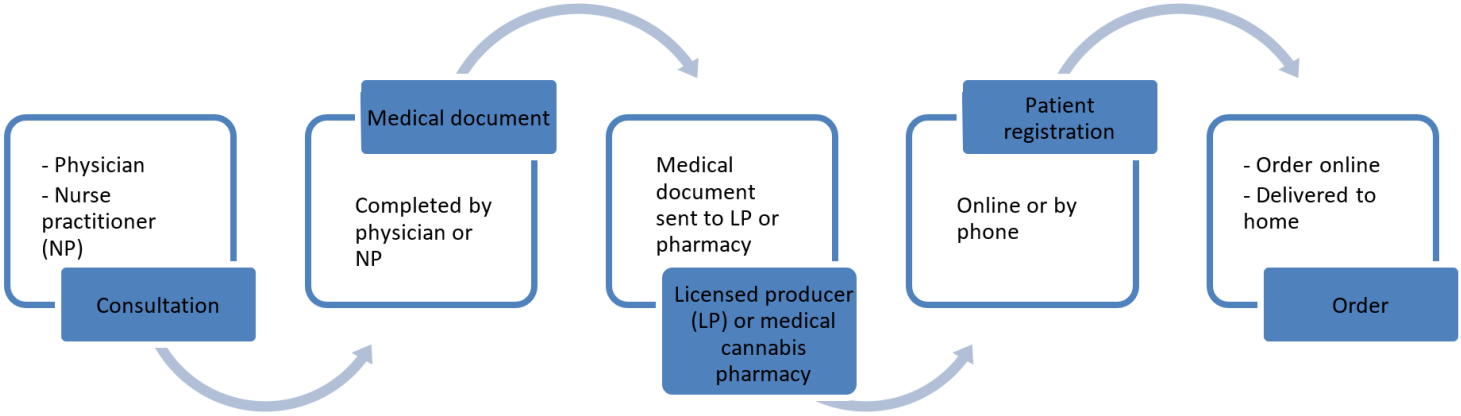

Figure 1: Obtaining cannabis is a multi-step process which requires steps to be taken by both the practitioner and patient. Patients/caregivers first meet with a physician or nurse practitioner (NP) who evaluates the indication for medical cannabis treatment. The physician or NP then completes a medical document which authorizes the patient or caregiver to obtain cannabis for the given indication. The medical document is submitted to a licensed producer (LP) or a medical cannabis pharmacy. The patient registers online or by phone with the LP or the pharmacy. After the medical document is approved and registration complete, the patient can now order cannabis from their respective location. The cannabis product is typically delivered to the patient's home or obtained at the pharmacy. Note: it is up to the authorizing physician or NP to instruct the patient which cannabis product to purchase.

Prior to prescribing, Health Canada recommends that physicians familiarize themselves with Information for Health Care Professionals, cannabis regulations, and the College of Physicians and Surgeons of Ontario's guidance on cannabis for medical purposes.

On the medical document, the following info must be included: (from section 273 of Cannabis Act)

(a) the health care practitioner's given name, surname, profession, business address and telephone number and, if applicable, their facsimile number and email address;

(b) the province in which the health care practitioner is authorized to practise their profession and the number assigned by the province to that authorization;

(c) the given name, surname and date of birth of the individual who is under the professional treatment of the health care practitioner;

(d) the address of the location at which the individual consulted with the health care practitioner;

(e) the daily quantity of dried cannabis, expressed in grams, that the health care practitioner authorizes for the individual; and

(f) a period of use, specified as a number of days, weeks or months.

Notes:

- The period of use specified in a medical document must not exceed one year.
- A medical document must be signed and dated by the health care practitioner who is providing it and must include a statement confirming that the information in the document is correct and complete.
- Daily quantity of dried cannabis can be determined by the mg/g content of the particular cannabis oil. This information can be provided by the licensed producers of the selected oil. If this calculation is uncertain or the information is not available, then daily allotments of 3 g/day will be enough to cover average daily doses of CBD & THC in the treatment of epilepsy.

Appendix 9: Components of the APE2 score and RITE2 score (Dubey et al., 2017)

Antibody Prevalence in Epilepsy and Encephalopathy (APE2) score	Value	Response to Immunotherapy in Epilepsy and Encephalopathy (RITE2) score	Value
New-onset, rapidly progressive mental status changes that developed over 1–6 weeks or new-onset seizure activity (within 1 year of evaluation)	(+1)	New-onset, rapidly progressive mental status changes that developed over 1–6 weeks or new-onset seizure activity (within 1 year of evaluation)	(+1)
Neuropsychiatric changes: agitation, aggressiveness, emotional lability	(+1)	Neuropsychiatric changes: agitation, aggressiveness, emotional lability	(+1)
Autonomic dysfunction (sustained atrial tachycardia or bradycardia, orthostatic hypotension, hyperhidrosis, persistently labile blood pressure, ventricular tachycardia, cardiac asystole or gastrointestinal dysmotility)*	(+1)	Autonomic dysfunction (sustained atrial tachycardia or bradycardia, orthostatic hypotension, hyperhidrosis, persistently labile blood pressure, ventricular tachycardia, cardiac asystole or gastrointestinal dysmotility)*	(+1)
Viral prodrome (rhinorrhea, sore throat, low-grade fever) to be scored in the absence of underlying systemic malignancy within 5 years of neurological symptom onset	(+2)	Viral prodrome (rhinorrhea, sore throat, low-grade fever) only to be scored in the absence of underlying malignancy within 5 years of neurological symptom onset	(+2)
Faciobrachial dystonic seizures	(+3)	Faciobrachial dystonic seizures	(+3)
Facial dyskinesias, to be scored in the absence of faciobrachial dystonic seizures	(+2)	Facial dyskinesias, to be scored in the absence of faciobrachial dystonic seizures	(+2)
Seizure refractory to at least to two antiseizure medications	(+2)	Seizure refractory to at least to two antiseizure medications	(+2)
CSF findings consistent with inflammation† (elevated CSF protein > 50 mg/dL and/or lymphocytic pleocytosis > 5 cells/mcL, if the total number of CSF RBC is < 1000 cells/mcL)	(+2)	CSF findings consistent with inflammation† (elevated CSF protein > 50 mg/dL and/or lymphocytic pleocytosis > 5 cells/mcL, if the total number of CSF RBC is < 1000 cells/mcL)	(+2)
Brain MRI suggesting encephalitis (T2/FLAIR hyperintensity restricted to one or both medial temporal lobes, or multifocal in gray matter, white matter, or both compatible with demyelination or inflammation)	(+2)	Brain MRI suggesting encephalitis (T2/FLAIR hyperintensity restricted to one or both medial temporal lobes, or multifocal in gray matter, white matter, or both compatible with demyelination or inflammation)	(+2)
Systemic cancer diagnosed within 5 years of neurological symptom onset (excluding cutaneous squamous cell carcinoma, basal cell carcinoma, brain tumor, cancer with brain metastasis)	(+2)	Systemic cancer diagnosed within 5 years of neurological symptom onset (excluding cutaneous squamous cell carcinoma, basal cell carcinoma, brain tumor, cancer with brain metastasis)	(+2)
		Immunotherapy initiated within 6 months of symptom onset	(+2)
		Neural plasma membrane autoantibody detected (NMDAR, $GABA_A$R, $GABA_B$R, AMPAR, DPPX, mGluR1, mGluR2, mGluR5, LGI1, IgLON5, CASPR2 or MOG)	(+2)

Scores are the sum of values for all components.

*Scored only if no history of autonomic dysfunction prior to onset of suspected autoimmune syndrome and the autonomic dysfunction not attributable to medications, hypovolemia, plasmapheresis, or infection

†Patients scored zero if brain MRI or CSF analysis not performed

AMPAR = amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CASPR2 = contactin-associated protein 2; DPPX = dipeptidyl-peptidase-like protein 6; FLAIR = fluid-attenuated inversion recovery; $GABA_A$R = γ-aminobutyric acid A receptor; $GABA_B$R = γ-aminobutyric acid B receptor; LGI1 = leucine-rich glioma-inactivated protein 1; MOG = myelin oligodendrocyte glycoprotein; mGluR1 = metabotropic glutamate receptor 1; mGluR5 = metabotropic glutamate receptor 5; NMDAR = N-methyl-D-aspartate receptor

Appendix 10: Antibodies contributing to focal epilepsy signs and symptoms (ACES) score (de Bruijn et al., 2021)

Value

Antibodies contributing to focal epilepsy signs and symptoms (ACES) score (de Bruijn et al., 2021)	Point
Cognitive symptoms	1
Behavioral changes	1
Autonomic symptoms	1
Speech problems	1
Autoimmune diseases	1
Temporal MRI hyperintensities	1

Appendix 11: Epilepsy Implementation Task Force Membership

Name	Title/Role	Organization
Dr. Carter Snead (Co-Chair)	Paediatric Neurologist	The Hospital for Sick Children
Brenda Flaherty (Co-Chair)	Executive Vice President & Chief Operating Officer	Hamilton Health Sciences
Dr. Sharon Whiting	Paediatric Neurologist	Children's Hospital of Eastern Ontario
Megan Wright	Chief Nurse Executive	Children's Hospital of Eastern Ontario
Mary Secco	Director of Strategic Initiatives	Epilepsy Support Centre
Rosalee (Rosie) Smith	Director of Adult Services	Epilepsy Toronto
Dr. Laurene Sellers	Family Practice Physician	Grand River Hospital Corporation
Dr. Michelle Shapiro	Adult Epileptologist	Hamilton Health Sciences
Kathryn LeBlanc	Director, Neurosciences	Hamilton Health Sciences
Louise MacRae	Director, Regional Stroke Program	Hamilton Health Sciences
David McNeil	Vice President Clinical Programs/CNO	Health Sciences North
Dr. Salil Gupta	Epileptologist	Health Sciences North
Dr. Athen MacDonald	Paediatric Neurologist	Kingston General Hospital
Dr. De Ribaupierre	Paediatric Neurosurgeon	London Health Sciences Centre
Dr. Jorge Burneo	Adult Neurologist	London Health Sciences Centre
Laurie Gould	EVP Patient-Centered Care	London Health Sciences Centre
Dr. Rajesh RamachandranNair	Paediatric Neurologist	McMaster Children's Hospital/HHS
Kirk Nylen	Manager, Knowledge Translation/Ops	Ontario Brain Institute
Liz Ferguson	Director, Centre for Brain and Behavior	The Hospital for Sick Children
Mike Tierney	VP Clinical Programs	The Ottawa Hospital
Dr. Hassan	Neurologist	Thunder Bay Regional Health Sciences Centre
Dr. Taufik Valiante	Adult Neurosurgeon	University Health Network
Janet Newton	Clinical Director	University Health Network

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