



Clinical Guidelines for the Management of Epilepsy in Adults and Children



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

Provincial Guidelines for the Management of Epilepsy in Adults and Children 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. The EITF works 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.

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

How to Use This Document

The Guidelines included in this document have been developed 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.

For information about these Guidelines, please contact:

EpLink – The Epilepsy Research Program of the Ontario Brain Institute



THE EPILEPSY RESEARCH PROGRAM
OF THE ONTARIO BRAIN INSTITUTE

Phone:
416-978-6381

Email:
info@eplink.ca
info@ontarioepilepsyguidelines.ca

Websites:
www.ontarioepilepsyguidelines.ca
www.eplink.ca

CCSO and the Ontario Brain Institute are funded by the Government of Ontario.



Version control

Name of document	Provincial Guidelines for the Management of Epilepsy in Adults and Children
Version 2.0	Created March 2020
Recommended next review	March 2023
Approved By	The Epilepsy Implementation Task Force (EITF) and EpLink - The Epilepsy Research Program of the Ontario Brain Institute

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.*

Acknowledgements

EpLink would like to thank the following individuals for their contribution to the development of this revision:

Name	Title/Role	Organization
Dr. Jorge Burneo	Co-Chair, Adult Epileptologist	London Health Sciences Centre
Dr. Rajesh RamachandranNair	Co-Chair, Pediatric Epileptologist	McMaster Children's Hospital
Dr. Carter Snead	Paediatric Neurologist	The Hospital for Sick Children

Please see Appendix 1 for a list of the original EITF membership.



List of Abbreviations

ASD	Anti-seizure drug (also known as anti-epileptic or anticonvulsant drug)
CBT	Cognitive Behavioural Therapy
CPSO	College of Physicians and Surgeons of Ontario
CPO	College of Psychologists of Ontario
CSF	Cerebral Spinal Fluid
CT	Computed Tomography
ECG	Electrocardiography
ED	Emergency Department
EEG	Electroencephalography
EMU	Epilepsy Monitoring Unit
EITF	Epilepsy Implementation Task Force
FHP	First Healthcare Provider
FP	Family Physician
GP	General Practitioner
ILAE	International League Against Epilepsy
LP	Lumbar Puncture
MRI	Magnetic Resonance Imaging
NP	Nurse Practitioner
OC	Oral Contraception
OCSWSSW	Ontario College of Social Workers and Social Service Workers
PNES	Psychogenic non-epileptic seizures
PNO	Provincial Neurosurgery Ontario
PWE	People with epilepsy
SSRI	Selective serotonin reuptake inhibitor
SNRI	Selective norepinephrine reuptake inhibitor
TDM	Therapeutic Drug Monitoring
WWE	Women with epilepsy



Definitions

Adolescent	A person 13 to 17 years of age.
Adolescent Medicine Specialist	Paediatrician practising adolescent medicine.
Child	A person less than 18 years of age.
Community Epilepsy Agencies	Community Epilepsy Agencies 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.
Epileptologist	<p>Qualifications and Training:</p> <ol style="list-style-type: none"> 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	An epileptic seizure is 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	<p>Epilepsy is a disease of the brain defined by any of the following conditions:</p> <ol style="list-style-type: none"> 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)
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.



Definitions

Medically Refractory Epilepsy	Failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drugs (whether as monotherapy or in combination) to achieve sustained seizure-freedom (Kwan, 2010 from International League Against Epilepsy).
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
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.
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.



This document is a partial update of “Clinical Guidelines for the Management of Epilepsy in Adults and Children” published by the Epilepsy Implementation Task Force in 2015. It updates the diagnosis, drug treatment and women with epilepsy sections of the 2015 guidelines and includes new recommendations for SUDEP, depression, stigma and psychogenic non-epileptic seizures.

CONTENTS

1. INTRODUCTION	9
1.1 Epilepsy Implementation Task Force	9
1.2 Epilepsy Care in Ontario	10
1.3 About this Document	11
1.4 Target Audience	11
1.5 The EITF Guidelines Series	12
2. KEY POINTS FROM THIS DOCUMENT	13
3. DIAGNOSIS OF EPILEPSY	14
3.1 Definitions	14
3.2 Classification of Epileptic Seizures	14
3.3 Types of Epilepsy Depending on Underlying Etiology	15
4. INITIAL EVALUATION	16
4.1 Clinical Diagnosis of Epileptic Seizures	16
4.2 Guideline on Initial Laboratory Tests After First Afebrile Seizure or New Onset Epilepsy	17
4.3 Guideline on Lumbar Puncture	17
4.4 Guideline on Neuroimaging in Adult and Pediatric Patients After First Afebrile Seizure or New Onset Epilepsy	17
4.4.1 Magnetic Resonance Imaging	17
4.4.2 Computed Tomography Scan	18
4.4.3 Electroencephalography	18
4.5 Genetic Testing	19
4.6 Guidelines for Other Tests	19
5. PSYCHOGENIC NON-EPILEPTIC SEIZURES	19
5.1 Prevalence and Diagnosis	19
5.2 Treatment	20
6. DRUG TREATMENT: GUIDELINE ON DRUG INITIATION AND MONITORING	21
6.1 Initiation of Antiseizure Drugs (ASDs) for the Treatment of Seizures in Epilepsy	21
6.2 Options for Antiseizure Drugs	22
6.3 Effect of ASDs on Hepatic Enzymes	24
6.4 Therapeutic Drug Monitoring	25
6.5 Other Blood Tests	25
6.6 Clinical Follow-up of Patients on ASD(s)	25
6.7 Discontinuation of ASD(s)	25



7. PATIENT EDUCATION AND COUNSELING	26
7.1 Patient Education	26
7.2 Role of Social Worker and Community Epilepsy Agency	26
7.3 Sudden Unexpected Death in Epilepsy (SUDEP)	27
7.4 Epilepsy Education Checklist	28
8. GUIDELINES FOR MANAGEMENT OF WOMEN WITH EPILEPSY WITH SPECIAL FOCUS ON PREGNANCY	29
8.1 Oral Contraception	29
8.2 Pregnancy	29
8.3 Placental Transfer and Teratogenicity	29
8.4 Valproic acid	30
8.5 Breastfeeding	31
8.6 Menopause	32
9. GUIDELINES ON REFERRING PATIENTS	32
9.1 From the Emergency Department	32
9.2 From General Practitioner/Family Physician	32
9.3 From Pediatricians/Internist	33
9.4 Referring Patients to Epileptologists	
9.4.1 Adult patients	33
9.4.2 Pediatric patients	33
9.5 Model for Co-management	33
9.5.1 Co-management of patients by GP/FP and the neurologist	33
9.5.2 Co-management of patients by pediatrician/internist and the neurologist	33
9.5.3 Co-management by Nurse Practitioners (NPs)	34
10. GUIDELINES ON FOLLOW UP	34
10.1 Patients Without Prolonged Seizure-Free Period	34
10.2 Patients After Prolonged Seizure-Free Interval	35
11. GUIDELINES ON COMORBIDITIES	35
11.1 Major comorbidities	35
11.2 Depression	35
11.3 Anxiety	37
11.4 Stigma	37
12. REFERENCES	38
APPENDIX 1: Original Epilepsy Implementation Task Force Membership	44
APPENDIX 2: Examples of Electroclinical Syndrome Arranged by Age at Onset	45
APPENDIX 3: ASD Dosing and Titration	46
APPENDIX 4: Outline for Seizure Assessment	48
APPENDIX 5: Ontario Community Epilepsy Agencies	49
APPENDIX 6: Description of Some of the Comorbidities Associated with Epilepsy	51



1. Introduction

Epilepsy affects around 95,000 Ontarians, of whom approximately 80,000 are adults and over 15,000 are children under the age of 18 (Institute for Clinical and Evaluative Sciences [ICES] & Ontario Brain Institute [OBI], 2015). While most individuals with epilepsy can be treated effectively by a primary care physician or general neurologist, an estimated 30% of those diagnosed have medically refractory epilepsy, experiencing seizures that do not respond to treatment with two or more appropriate antiepileptic drugs (Kwan & Brodie, 2000). These numbers are not static. Each year it is estimated that 6,500 Ontarians will develop epilepsy, and 1,950 of them will have medically refractory epilepsy (Tellez-Zenteno, Pondal-Sordo, Matijevic, & Wiebe, 2004; Wiebe, Bellhouse, Fallahay, & Eliasziy, 1999).

Epilepsy surgery has shown positive outcomes for epilepsy sufferers; there is approximately a 60% chance that an individual will be seizure-free after surgery, resulting in far better outcomes with respect to seizure freedom, improved quality of life, and reduction of psychosocial comorbidities that accompany medically refractory epilepsy than continued medical treatment (West et al., 2019; Bowen, Snead, Chandra, Blackhouse, & Goeree, 2012). However, not all individuals with epilepsy are candidates for surgery – approximately 50% of those suffering from medically refractory epilepsy will not be considered candidates.

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 (Burneo, Shariff, Liu, Leonard, Saposnik, & Garg, 2016). 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 low 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 Prov-

ince (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 39 (26 adult and 13 paediatric). The Ministry also resourced additional epilepsy surgery and vagal nerve stimulator capacity through the 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, Paediatric 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 Critical Care Services Ontario (www.criticalcareontario.ca). For a list of EITF membership, please see Appendix 1.



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 antiseizure drugs (ASDs), 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 except 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.

The following hospitals are classified as District Epilepsy Centres:

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

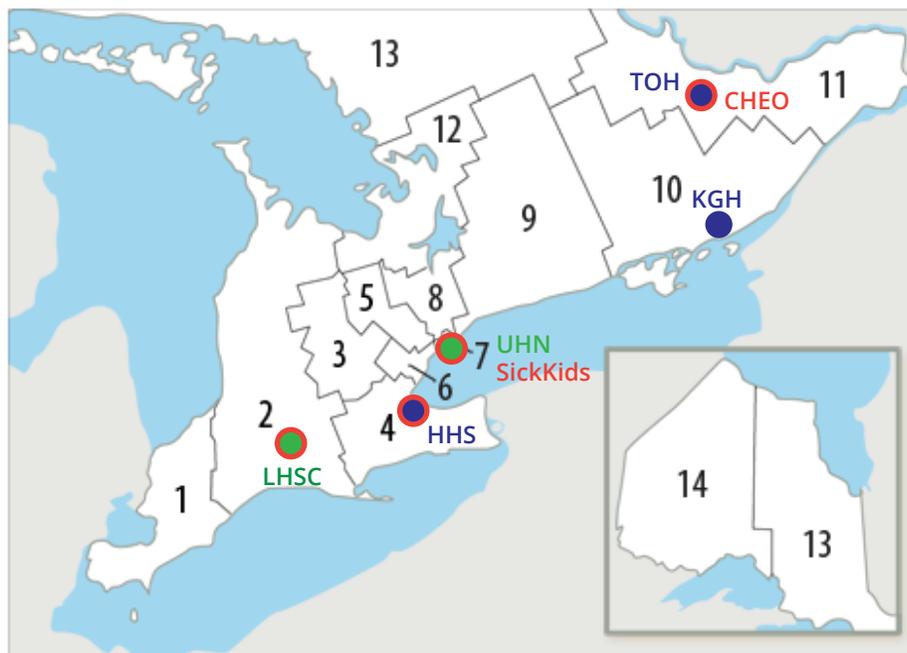
2. A Regional Epilepsy Surgery Centre of Excellence (RESC) is a facility with a comprehensive epilepsy program that provides all the services available in a DEC, and in addition, epilepsy surgery including facility for intracranial monitoring. An RESC is also a DEC for its catchment area.

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	-



Map of Ontario's Epilepsy Centres by Local Health Integration Networks (LHINs)



- District Epilepsy 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 includes, but is not limited to, family physicians (FP), nurse practitioners (NP), pediatricians, internists, emergency physicians, community epilepsy agencies and neurologists. The guidelines should be shared with anyone involved in the care of patients with epilepsy.



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; next review 2021)

This document provides an approach to referral of medically-refractory 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 Medically Refractory Epilepsy in Adults and Children Who are not candidates for Epilepsy Surgery (March 2016; next update 2021)

This guideline will provide an approach to the management of the patient with medically intractable epilepsy in whom surgical treatment is not an option. It will include the use of antiepileptic medications and non-antiepileptic therapy such as dietary management and neurostimulation.

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.



KEY POINTS FROM THIS DOCUMENT

DEFINITIONS

Epilepsy is a disease of the brain defined by any of the following conditions:

- ◆ At least two unprovoked (or reflex) seizures occurring >24 h apart
- ◆ 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
- ◆ Diagnosis of an epilepsy syndrome

CLASSIFICATION OF SEIZURES

- ◆ Seizure onset can be classified as generalized, focal or unknown with motor, non-motor or unclassified features
- ◆ An epilepsy syndrome refers to a cluster of features incorporating seizure types, EEG, and imaging features that tend to co-occur
- ◆ The Idiopathic Generalized Epilepsies encompass Childhood Absence Epilepsy, Juvenile Absence Epilepsy, Juvenile Myoclonic Epilepsy and Generalized Tonic-Clonic Seizures Alone

INITIATION OF ASD TREATMENT

- ◆ The choice of anti-seizure drug (ASD) depends on multiple patient- and drug-specific variables
- ◆ Patients should be treated with a single drug when possible
- ◆ Combination therapy should only be considered when monotherapy does not provide seizure freedom
- ◆ ASD interactions and comorbidities should be taken into consideration when choosing combination therapy

DRUG-RESISTANT EPILEPSY

- ◆ Any patient who is not seizure-free after two adequate trials of ASDs (either alone or in combination) is considered drug-resistant and should be referred for epilepsy surgery evaluation
- ◆ Patients can be referred to a District Epilepsy Centre or Regional Epilepsy Surgical centre for a comprehensive assessment
- ◆ Centres are located in Toronto, Hamilton, Ottawa, London, Kingston and Sudbury

WOMEN WITH EPILEPSY

- ◆ Discuss plans for pregnancy with women of childbearing age
- ◆ Avoid enzyme-inducing ASDs in women with epilepsy using oral contraceptives, transdermal patches, or levonorgestrel implants
- ◆ Whenever possible, valproic acid should be avoided in women of childbearing potential due to the risk of teratogenicity and neurodevelopmental delays
- ◆ Folic acid supplements (0.4 - 4 mg/day) are recommended before and during pregnancy

SUDEP

- ◆ The incidence of sudden death is estimated to be approximately 11.2 cases per 1000 individuals with epilepsy per year
- ◆ Seizure freedom, particularly freedom from generalized tonic-clonic seizures, is strongly associated with decreased SUDEP risk
The risk may be reduced by lowering seizure frequency and by adherence to ASD treatment
- ◆ Patients and families prefer to have the initial discussion about SUDEP with their neurologist

EPILEPSY EDUCATION

- ◆ Health care providers are encouraged to provide their patients with the contact information of their local Community Epilepsy Agency
- ◆ Families should be provided with clear, accurate and timely information about their condition and how they can access needed resources
- ◆ Important topics include school and employment concerns, driving, reproductive health, drug interactions and medication side effects

REFERRING PATIENTS

- ◆ Patients presenting to the emergency department with a first seizure should follow up with their family physician
- ◆ Patients should be referred for an EEG, and if necessary MRI brain, after the first unprovoked seizure
- ◆ Patients who fail to respond to an adequate trial of the first ASD should be referred to a neurologist
- ◆ All patients in Ontario with medically refractory focal seizures should be referred to an epileptologist

COMORBIDITIES

- ◆ Depression and anxiety are common in people with epilepsy
- ◆ Patients should be regularly screened for depression and offered supportive therapy
- ◆ Antidepressant use is generally safe in patients with epilepsy when used at therapeutic doses
- ◆ Neurodevelopmental disorders, including autism, ADHD and intellectual disability are associated with epilepsy, and health care providers should actively assist families to access appropriate services



3. Diagnosis of Epilepsy

3.1 Definitions

Epileptic Seizure: An epileptic seizure is 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 (Fisher et al., 2014):

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

Epileptic seizures and epilepsy in patients are best classified using a multi-axial diagnostic scheme (when possible) (National Institute for Health and Clinical Excellence [NICE], 2012). Axes that should be considered are:

- Seizure type;
- Description of seizure (ictal phenomenology);
- Syndrome; and
- Etiology

3.2 Classification of Epileptic Seizures

(Scheffer et al., 2017):

a) Generalized onset seizures: Generalized epileptic seizures are conceptualized as originating at some point within, and rapidly engaging, bilaterally distributed networks. Such bilateral networks do not necessarily include the entire cortex. Generalized seizures can be asymmetric.

b) Focal onset seizures: Focal epileptic seizures are conceptualized as originating within networks limited to one hemisphere. Recognition of impairment of awareness or other features, localization, and progression of ictal events can be of primary importance in the evaluation of individual patients and for specific purposes (e.g., differential diagnosis of

non-epileptic events from epileptic seizures, randomized ASD trials, and surgery).

c) Unknown onset: A seizure that cannot be clearly diagnosed into one of the preceding categories should be considered of unknown onset or unclassified until further information allows their accurate diagnosis.

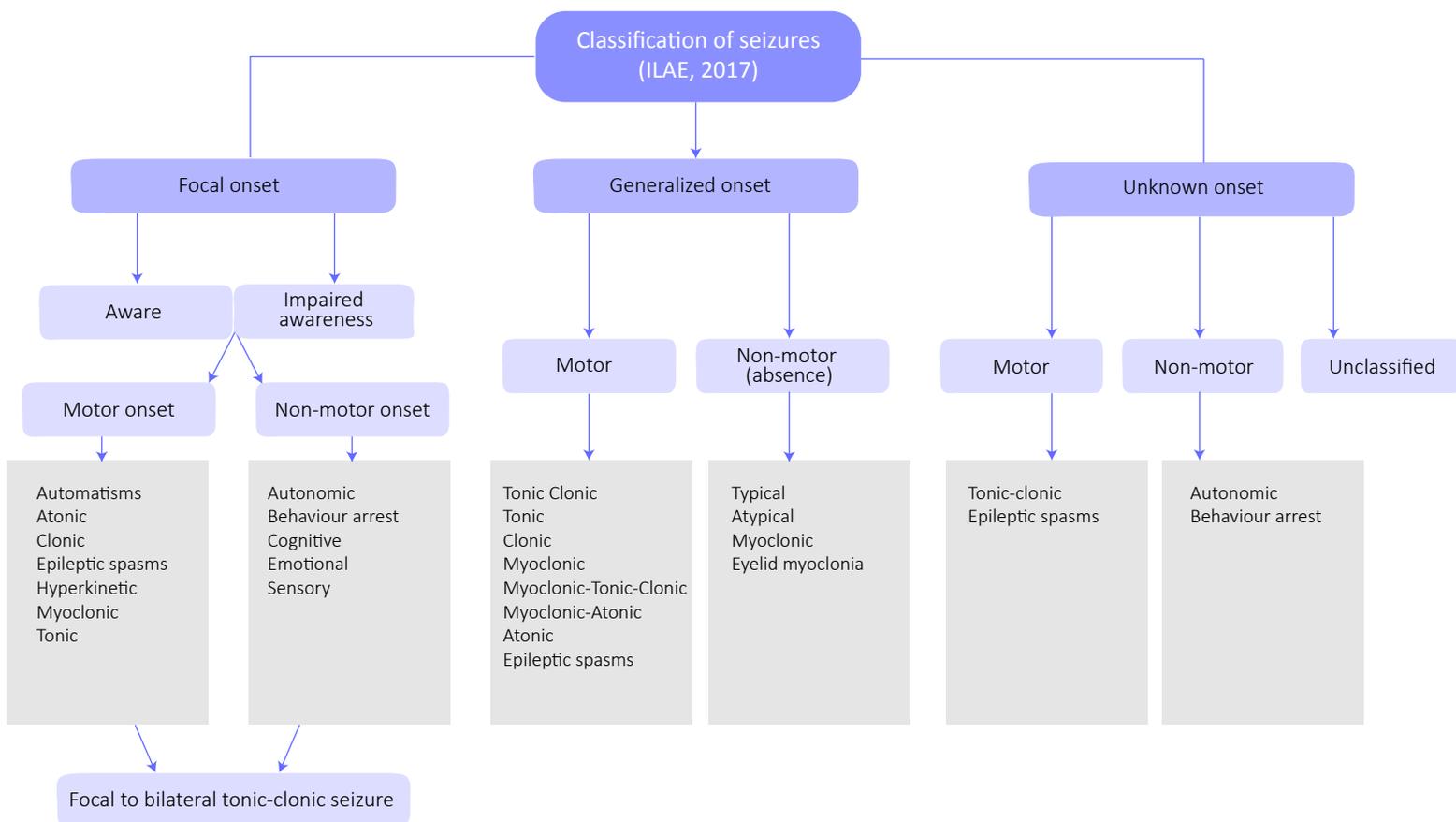
Please note, this is not considered a classification category.

Electroclinical Epilepsy Syndrome: An epilepsy syndrome refers to a cluster of features incorporating seizure types, EEG, and imaging features that tend to occur together. It often has age-dependent features such as age at onset and remission (where applicable), seizure triggers, diurnal variation, and sometimes prognosis. It may also have distinctive comorbidities such as intellectual and psychiatric dysfunction, together with specific findings on EEG and imaging studies. A group of clinical entities that are reliably identified by a cluster of electroclinical characteristics (i.e. age, seizure types, EEG characteristics). There are many well-recognized syndromes, such as childhood absence epilepsy, West syndrome, and Dravet syndrome. Patients whose epilepsy does not fit the criteria for a specific electroclinical syndrome can be described with respect to a variety of clinically relevant factors, such as known etiology and seizure types (Berg et al., 2010.) For more information, please see Appendix 2: Examples of Electroclinical syndrome arranged by age at onset.

Idiopathic Generalized Epilepsies: Within the Generalized Epilepsies is the well-recognized and common subgroup of the Idiopathic Generalized Epilepsies (IGEs). The IGEs encompass four well-established epilepsy syndromes: Childhood Absence Epilepsy, Juvenile Absence Epilepsy, Juvenile Myoclonic Epilepsy and Generalized Tonic-Clonic Seizures Alone (formerly known as Generalized Tonic-Clonic Seizures on Awakening but modified in recognition that seizures can occur at any time of day). In individual cases, the term Genetic Generalized Epilepsy may be used where the clinician is comfortable with invoking a genetic etiology.



Figure 1: Classification of Seizures



3.3 Types of Epilepsy Depending on Underlying Etiology (updated 2020)
(Scheffer et al., 2017)

a) Structural: Conceptually, there is a distinct structural abnormality or disease that has been demonstrated to be associated with a substantially increased risk of developing epilepsy in appropriately designed studies. Examples include stroke and trauma.

b) Genetic: The concept of a genetic epilepsy is that it results directly from a known or presumed genetic mutation in which seizures are a core symptom of the disorder. The best known example is Dravet syndrome, in which >80% of patients have a pathogenic variant of the SCN1A gene. It is important to note that genetic does not equate with inherited. An increasing number of de novo mutations are being identified in both severe and mild epilepsies, mean-

ing that the patient has a new mutation that has arisen in him or her that may now be a heritable form of epilepsy.

c) Metabolic: The concept of a metabolic epilepsy is that it results directly from a known or presumed metabolic disorder in which seizures are a core symptom of the disorder. Metabolic causes refer to a well-delineated metabolic defect with manifestations or biochemical changes throughout the body such as porphyria, uremia, aminoacidopathies, or pyridoxine-dependent seizures. In many cases, metabolic disorders will have a genetic defect. It is likely that most metabolic epilepsies will have a genetic basis, but some may be acquired such as cerebral folate deficiency.



d) **Infectious:** The most common etiology worldwide is where epilepsy occurs as a result of an infection. The concept of an infectious etiology is that it directly results from a known infection in which seizures are a core symptom of the disorder. Common examples in specific regions of the world include neurocysticercosis, tuberculosis, HIV, cerebral malaria, subacute sclerosing panencephalitis, cerebral toxoplasmosis, and congenital infections such as Zika virus and cytomegalovirus.

e) **Immune:** The concept of an immune epilepsy is that it results directly from an immune disorder in which seizures are a core symptom of the disorder. An immune etiology can be conceptualized as where there is evidence of autoimmune-mediated central nervous system inflammation. Examples include anti-NMDA (N-methyl-D-aspartate) receptor encephalitis and anti-LGI1 encephalitis.

f) **Unknown cause:** Unknown is meant to be viewed neutrally and to designate that the nature of the underlying cause is as yet unknown; it may have a fundamental genetic defect at its core or it may be the consequence of a separate as yet unrecognized disorder.

4. Initial Evaluation

After their first unprovoked epileptic seizure, patients are typically evaluated by ED physicians or in a clinic setting by a nurse practitioner, family physician, internist, pediatrician or neurologist. These first healthcare providers (FHP) are responsible for the initial and/or continued management of patients.

Identification of coexisting conditions or disorders causing seizures requiring emergency department (ED) diagnosis and treatment is beyond the scope of this document. Similarly, recommendations on the management of acute prolonged seizure are beyond the scope of this document. Each hospital should have a guideline in place for the management of

patients who present with acute prolonged seizures and require inpatient treatment and evaluation.

Although patients present in diverse situations, the FHP should provide as accurate a diagnosis as possible and appropriate information regarding their condition. A strategy in partnership with the patient, utilizing all currently available treatment options with the goal of abolishing seizures may not be possible at the first contact visit. Patients should be educated about their condition and encouraged to address factors under their control.

4.1 Clinical Diagnosis of Epileptic Seizures

The diagnosis of epilepsy should not be based on the presence or absence of single features. The clinical decision as to whether an epileptic seizure has occurred should be based on the combination of the description of the event, associated symptoms and ancillary information. A detailed history should be taken from the child, young person or adult and an eyewitness to the clinical event, where possible, to determine whether or not an epileptic seizure is likely to have occurred (see Appendix 4). A careful history and neurologic examination may allow a diagnosis without extensive further evaluation.

It may not be possible to make a definite diagnosis of epilepsy initially. If the diagnosis cannot be clearly established, referral to an appropriate specialist should be considered.

Misdiagnosis of epilepsy has several implications (Ferrie, 2006) including:

- Misuse of available resources for epilepsy treatment
- Restrictions on activities are commonly applied and educational expectations and employment prospects may be lowered
- Patients who are misdiagnosed are treated with ASDs that have adverse effects



- Treatable serious conditions are overlooked
- Benign conditions, for which treatment is reassurance, are neglected
- Concerns regarding the standard of care may be raised

Episodic disorders including but not limited to: syncope, migraine, drug reaction or intoxication, and mental disorders such as psychogenic seizures may be confounders at first contact (Zaidi, Clough, Cooper, Scheepers, & Fitzpatrick, 2000). When psychogenic seizures are suspected, suitable referral should be made to psychological or psychiatric services for further investigation and treatment.

Examination: A clinical examination that includes a neurologic examination is essential, since an abnormal examination after a first seizure also predicts recurrence (Berg, 2008). This should address their cardiac, neurological and mental status, and should include a developmental assessment where appropriate.

Reporting: While confidentiality is to be maintained, there is a duty of mandatory reporting in Canada and Ontario imposed on the FHP. These are primarily, but not exclusively, limited to notification of the Ministry of Transportation. This is more extensively covered under:

<https://www.cpso.on.ca/Physicians/Policies-Guidance/Policies/Mandatory-and-Permissive-Reporting#impaired>

4.2 Guideline on Initial Laboratory Tests After First Afebrile Seizure or New Onset Epilepsy

Adults: A basic panel to assess electrolytes and complete blood count, as well as drug screen, are a consideration in patients with a first-time seizure to rule out the possibility of a provoked seizure. However, there are no prospective studies that demonstrate a benefit of routine use. Individual consideration should be given to the circumstances (College of Emergency Medi-

cine [CEM], 2009). The ED presentation may require knowledge of pregnancy status to enable informed treatment decisions.

Children: Laboratory tests should be ordered based on individual clinical circumstances that include suggestive historic or clinical findings such as vomiting, diarrhea, dehydration, or failure to return to baseline alertness. Toxicology screening should be considered across the entire paediatric age range if there is any question of drug exposure or substance abuse (Hirtz et al., 2000).

4.3 Guideline on Lumbar Puncture

In the very young child (<6 months), in the child of any age with persistent (cause unknown) alteration of mental status or failure to return to baseline, or in any child with meningeal signs, lumbar puncture (LP) should be performed. If increased intracranial pressure is suspected, the LP should be preceded by an imaging study of the head (Hirtz et al., 2000).

In adults, the LP should be considered only if there is a suspicion for an infection of the Central Nervous System (Krumholz et al., 2007). It should not be part of a routine assessment.

4.4 Guideline on Neuroimaging in Adult and Pediatric Patients After First Afebrile Seizure or New Onset Epilepsy

Brain imaging should be considered as part of the neurodiagnostic evaluation of adults presenting with an apparent unprovoked first seizure (Krumholz et al., 2007).

4.4.1 Magnetic Resonance Imaging (MRI)

MRI is the preferred neuroimaging method in adults and children presenting with first afebrile seizure, although MRIs may not be readily available for urgent neuroimaging in some situations. In adults, MRI may be considered to be done at a later time, if the neurological examination is non-focal.



Non-urgent imaging studies with MRI should be seriously considered in any child with a significant cognitive or motor impairment of unknown etiology, unexplained abnormalities on neurologic examination, a seizure of focal onset with or without secondary generalization, an EEG that does not represent a benign focal epilepsy of childhood or primary generalized epilepsy, or in children under 2 year of age (Hirtz et al., 2000; Gaillard et al., 2009). MRI has far better resolution for developmental anomalies of the brain that lead to epilepsy in children (e.g. focal cortical dysplasia) than a computed tomography scan.

4.4.2 Computed Tomography (CT) Scan

Given the potential for intracranial bleeds, strokes, and brain tumors to present with seizures in adults, an emergent CT scan may be considered in adults with first seizure, in certain situations. The clinical and historical features of an abnormal neurologic examination or a focal seizure onset are probably predictive of an abnormal CT study for patients presenting with seizures in the emergency department.

An emergency CT should be considered in children presenting with first afebrile seizure in the emergency department who have:

- an abnormal neurologic examination;
- predisposing history (age less than 6 months, closed head injury, recent cerebral spinal fluid [CSF] shunt revision, malignancy, or neurocutaneous disorder); or
- focal seizure onset (Harden et al., 2007)

The evidence is inadequate to support the usefulness of emergency CT in persons with chronic seizures. There is no recommendation regarding an emergency CT in persons with chronic seizures (Harden et al., 2007).

4.4.3 Electroencephalography (EEG)

i. Considered as part of the neurodiagnostic

evaluation of the adult with an apparent unprovoked first seizure because it has a substantial yield and has value in determining the risk for seizure recurrence (Krumholz, 2007).

ii. Recommended as part of the neurodiagnostic evaluation of the child with an apparent first unprovoked seizure (Hirtz et al., 2000).

iii. There is no evidence that the EEG must be done before discharge from the emergency department; the study may be arranged on an elective outpatient basis, unless there is a concern for non-convulsive status epilepticus.

iv. Epileptiform abnormalities on the EEG may be useful in confirming that the event was a seizure; however, an EEG abnormality by itself is not sufficient to make a diagnosis that an epileptic seizure occurred, nor can its absence rule out a seizure (Vining & Freeman, 1986; Holmes, 1988).

v. An EEG is necessary to determine the epilepsy syndrome and the diagnosis of an epilepsy syndrome may be helpful in determining the need for imaging studies and specific ASD treatment.

vi. An EEG is useful in predicting the prognosis for recurrence of seizures (Panayiotopoulos, 1998; Vining & Freeman 1986; Holmes, 1988).

vii. An EEG done within 24 hours of the seizure is most likely to show abnormalities. Physicians should be aware that some abnormalities such as postictal slowing that can be seen on an EEG done within 24 to 48 hours of a seizure may be transient and must be interpreted with caution (Hirtz et al., 2000).

viii. Repeated standard EEGs should not be used in preference to sleep or sleep-deprived EEGs. When a standard EEG has not contributed to diagnosis or classification, a sleep EEG can be considered if clinically indicated. In children and young people, a sleep EEG is best achieved through sleep deprivation or the use of melatonin (NICE, 2012).



EEGs should be performed in accordance with the guidelines endorsed by the Canadian Society of Clinical Neurophysiologists (CSCN). Revised guidelines were published in 2017 (Dash et al., 2017).

4.5 Genetic Testing

Every day brings a new understanding of the genetic basis of epilepsy (Perry 2020). A number of studies now show that next generation sequencing (NGS)-based strategies can provide a molecular diagnosis in 15-30% of individuals with epilepsy and, for specific clinical presentations (Jain et al., 2019), the rate can be much higher (Mercimek-Mahmutoglu et al., 2015; Myers et al., 2019). As a result, the application of NGS has rapidly transformed the way in which genetic epilepsy is diagnosed. The sequencing of dozens to even hundreds of genes, is now commercially available with a wide variety of “epilepsy panels” available through commercial laboratories (Chambers, Jansen & Dhamija, 2016).

The benefits of a molecular diagnosis for epilepsy include guiding a direction of treatment towards disease-modifying therapies and/or medications known to be effective in certain epilepsy syndromes, and clarification of the long-term prognosis and limitation of further diagnostic investigations that have associated risks and costs. A genetic diagnosis also provides informed genetic counselling purposes and potential prenatal testing options. As well, a genetic diagnosis is hugely important for families who have long faced a fruitless search for an etiology, putting their minds at rest and thus providing a psychosocial benefit to the individual and their families (Jain et al., 2018; Dymment et al. 2019).

Recently, an expert Working Group of medical geneticists, pediatric neurologists/ epileptologists, biochemical geneticists and clinical laboratory scientists from Ontario was formed by the Laboratories and Genetics Branch of the Ontario Ministry of Health to develop a pro-

grammatic approach to implementing epilepsy panel testing as a provincial service. This Working Group made several recommendations for testing, including that any gene panel testing must be “evidence-based” and take into account varied clinical indications and reduces the chance of uncertain and secondary results (Dymment et al., 2019). This epilepsy panel testing implementation plan promises to be a model for genetic care directed towards a specific set of conditions in the province and will provide a prototype for genetic testing for other diseases and strategies.

4.6 Guidelines for Other Tests

Seizure-like attacks with a cardiovascular cause may be misdiagnosed as epilepsy. A 12-lead electrocardiography (ECG) should be performed in adults with suspected epilepsy. In children and young people, a 12-lead ECG should be considered in cases of diagnostic uncertainty (Stokes, Shaw, Juarez-Garcia, Camosso-Stefinovic, & Baker, 2004; MacCormick et al., 2009).

5. Psychogenic non-epileptic seizures (updated 2020)

5.1 Prevalence and Diagnosis

Psychogenic, non-epileptic seizures (PNES) are paroxysmal events that resemble epileptic seizures (ES) but are not associated with epileptiform discharges on electroencephalogram (EEG). PNES patients account for up to 40% of patients evaluated in epilepsy monitoring units and occur in both pediatric and adult populations. Accurate diagnosis can be challenging since up to 10% of patients will present with a combination of ES and PNES (LaFrance et al., 2013).

PNES are multifactorial and no single clinical feature is pathognomonic for this condition.



However, traumatic events in childhood or adult life have been identified as a predisposing factor, with up to 70% of patients (Hopp, 2019). Psychiatric comorbidities are very common, and estimates suggest that between 53 and 100% of PNES patients present with at least one comorbid psychiatric disorder (Bompaire et al., 2019), most commonly depression, anxiety, posttraumatic stress disorder or personality disorders. 75% of patients with PNES are young adult women, although female predominance is classically not found in children, where the most common precipitating factors are school phobia or difficulties in school (including bullying, specific learning difficulties, or unrealistic expectations) (Bompaire et al., 2019).

The gold standard diagnosis of PNES is based on a history consistent with PNES and the video-EEG recording of a typical event with semiological features of PNES but no epileptiform activity before, during, or after the event. However, caution must be taken as not all seizures are associated with clear EEG changes (e.g. in frontal lobe epilepsy).

- Signs that favour the diagnosis of PNES vs ES include female gender, family history of epilepsy (modeling), childhood physical or sexual abuse, traumatic brain injury (with comorbid depression, behavioral impulsivity, or posttraumatic stress disorder), medical comorbidities, and brain dysfunction.
- Clinical features associated with PNES and not ES are: Writhing, flailing, and whole-body thrashing; eye-blinking, swallowing, and slumping; intelligible speech; eyes closed at seizure onset; forced eye closure, ictal crying, gradual onset, asynchronous movements, pelvic thrusting, recall during the period of apparent unresponsiveness, and hyperventilation.
- Clinical features associated with ES and not PNES are postictal focal neurological deficits, altered breathing, somatic complaints, increased HR, altered pupillary response, and increased serum prolactin.

- Tongue bites are often located laterally in patients with epileptic seizures, whereas patients with PNES may experience tip-of-the-tongue, lip or buccal bites (Devinsky et al, 2011).

5.2 Treatment

- Physicians should be clear, honest and encouraging when presenting a diagnosis of PNES. Emphasize the positive news that the patient does not have epilepsy and does not require ASDs, that the disorder is real, and outline plans for further evaluation and treatment.
- If evaluation has suggested the presence of a mental health disorder, then a referral should be made to the appropriate provider.
- In patients with solely PNES, ASD treatment can be discontinued unless a specific ASD has a documented beneficial psychopharmacologic effect. In people with mixed ES/PNES, reduce high doses of ASDs or polytherapy if possible (Kerr et al., 2011).
- Cognitive behavioural therapy (CBT) may be a first-line psychological treatment in adults and the elderly with PNES (Gasparini et al., 2019). Care should be coordinated between the multidisciplinary health care providers (e.g., neurologist and mental health professional).
- Some patients may remit after receiving a diagnosis and/or receiving CBT, but a substantial number need longer-term psychotherapeutic or mental health interventions.
- Although high quality RCTs are lacking, evidence suggests that approximately half of PNES patients are seizure free following psychological intervention, while more than 80% experience a reduction in seizures of 50% or more (Carlson & Nicholson Perry, 2017).



- Physicians should be aware that patients may resist the diagnosis and that significant obstacles to treatment may remain, including delays in referrals for further testing and treatment; patients feeling abandoned by their neurologist; a lack of treatment providers with expertise in PNES and a lack of resources for psychological treatment.

6. Drug Treatment: Guideline on Drug Initiation and Monitoring

6.1 Initiation of Antiseizure Drugs (ASDs) for the Treatment of Seizures in Epilepsy

Treatment with ASDs in patients with epilepsy aims to provide the best quality of life with no seizures and fewest adverse effects from treatment (Glauser et al., 2006). The decision to initiate ASDs in patients with newly diagnosed epilepsy (including patients not currently on ASDs) should be based on the discussion between the physician and the patient (or legal guardian/ caregiver). This discussion should include the following:

- Risk of seizure recurrence
- Cost of treatment
- Type of seizures
- Potential duration of treatment
- Type of epilepsy and the natural course of epilepsy
- Negative effects of seizures
- ASD options
- Goals of treatment (including optimal seizure control target)
- Potential side effects of ASD(s)

The choice of ASD depends on multiple factors, including (Glauser et al. 2006; Donner & Snead, 2006):

- **Patient-specific variables:** age, gender, co-medications, co-morbidities, affordability/ insurance status, and ability to swallow pills/tablets

- **ASD-specific variables:** seizure or epilepsy syndrome, adverse effects, ease and speed of drug initiation, teratogenicity, interactions, pharmacokinetics, and availability

General Principles of ASD Treatment (NICE, 2012):

1. It is recommended that children, young people and adults should be treated with a single ASD (monotherapy) whenever possible.
2. If the initial treatment is unsuccessful, then monotherapy using another drug or add-on treatment with a second drug can be tried. Caution is needed during the changeover period. If an ASD has failed because of adverse effects or continued seizures, a second drug should be started (which may be an alternative first-line or second-line drug) and built up to an adequate or maximum tolerated dose and then the first drug may be tapered off slowly.
3. If the second drug is unhelpful, either the first or second drug may be tapered, depending on relative efficacy, side effects and how well the drugs are tolerated before starting another drug. Some patients are required to be on more than two ASDs.
4. It is recommended that combination therapy (adjunctive or 'add-on' therapy) should only be considered when attempts at monotherapy with the tolerated dose of ASD have not resulted in seizure freedom. If trials of combination therapy do not bring about worthwhile benefits, treatment should revert to the regimen (monotherapy or combination therapy) that has proved most acceptable to the child, young person or adult, in terms of providing the best balance between effectiveness in reducing seizure frequency and tolerability of side effects.
5. ASD interactions and comorbidities should be taken into consideration when choosing combination therapy.
6. If there is no improvement after two adequate trials of ASDs, the patient should be referred for epilepsy surgery evaluation.



6.2: Options for Anti-Seizure Drugs (listed alphabetically) (updated 2020)

(NICE, 2012; Glauser et al., 2006; Glauser et al., 2013; Health Canada, 2016; Kanner et al., 2018)

Note: This list is not exhaustive. Some of the

drugs can be used only for 'off label' purposes in Ontario. There are useful websites/resources that provide information on common ASDs. One example of such a resource is the National Centre for Biotechnology Information:

<http://www.ncbi.nlm.nih.gov/books/NBK2597/#ch1>

First-line ASDs	Adjunctive ASDs	Other ASDs that may be considered	Do not offer ASDs (may worsen seizures)
Adults with focal seizures			
Carbamazepine ^a Eslicarbazepine Lamotrigine Levetiracetam Oxcarbazepine Phenytoin Topiramate Valproic acid ^c	Brivaracetam Carbamazepine Clobazam ^b Eslicarbazepine Gabapentin ^b Lamotrigine ^b Levetiracetam Oxcarbazepine Perampanel Phenytoin Topiramate Valproic acid ^c	Phenobarbital Pregabalin	n/a
Adults with generalized tonic-clonic seizures			
Clobazam Lamotrigine Levetiracetam Perampanel Valproic Acid ^c	Clobazam Lamotrigine Levetiracetam Perampanel Phenobarbital Primidone Topiramate Valproic acid ^c		(If there are absence or myoclonic seizures, or if JME suspected) Carbamazepine ^a Gabapentin Oxcarbazepine Phenytoin Pregabalin
Children with focal seizures			
Carbamazepine ^a Clobazam Oxcarbazepine Phenobarbital Topiramate Valproic Acid ^c	Brivaracetam Levetiracetam		
Children with generalized tonic clonic seizures			
Carbamazepine ^a Lamotrigine Levetiracetam Phenobarbital Topiramate Valproic Acid ^c	Clobazam		Carbamazepine and Phenytoin may precipitate or aggravate generalized tonic clonic seizures.



First-line ASDs	Adjunctive ASDs	Other ASDs that may be considered	Do not offer ASDs (may worsen seizures)
Children with absence seizures			
Ethosuximide Valproic Acid ^c Lamotrigine can also be considered.	Ethosuximide Lamotrigine Valproic Acid ^c	Clobazam Clonazepam Levetiracetam Topiramate Zonisamide	Carbamazepine ^a Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Benign epilepsy of childhood with centrotemporal spikes			
Carbamazepine ^a Valproic Acid ^c Gabapentin, Clobazam, Levetiracetam and Oxcarbazepine are potentially effective.			
Myoclonic (including Juvenile Myoclonic Epilepsy)			
Lamotrigine Levetiracetam Topiramate Valproic Acid ^c	Lamotrigine Levetiracetam Perampanel Topiramate Valproic Acid ^c	Clobazam Clonazepam Zonisamide	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin
Infantile spasms			
Vigabatrin Steroids (Oral prednisolone/ injection adrenocorticotrophic hormone).		Topiramate Ketogenic diet	
Dravet syndrome			
Topiramate Valproic acid ^c	Clobazam Stiripentol		Carbamazepine ^a Gabapentin Lamotrigine Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin



First-line ASDs	Adjunctive ASDs	Other ASDs that may be considered	Do not offer ASDs (may worsen seizures)
Lennox-Gastaut syndrome			
Rufinamide Valproic acid ^c	Clobazam Lamotrigine Perampanel Rufinamide Topiramate		Carbamazepine Gabapentin Oxcarbazepine Pregabalin Tiagabine Vigabatrin
Children less than 1 year of age			
			Valproic acid
Children 1-2 years			
			Valproic acid (use with caution due to hepatotoxicity). This risk is high in combination with CYP inducers such as phenobarbital and phenytoin.

^a Severe allergic reactions, including Stevens Johnson Syndrome and toxic epidermal necrolysis, are possible with the use of Carbamazepine in certain ethnicities like Asians, especially Han Chinese (Grover & Kukreti, 2014; Jentink et al., 2010).

^b May be considered for elderly adults

^c Should not be used in women and girls of childbearing potential

Please see Appendix 3 for dosing and titration information.

6.3 Effect of ASDs on Hepatic Enzymes (updated 2020)

Most ASDs are metabolized and eliminated via hepatic cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT) enzymes. Since many ASDs also induce or inhibit the activity of these same enzymes, there is a significant risk of interactions for patients utilizing polytherapy.

- Carbamazepine, phenytoin, phenobarbital and primidone are the major enzyme-inducing ASDs that increase the clearance of most co-administered ASDs, including valproic acid, tiagabine, ethosuximide, lamotrigine, oxcarba-

zepine, zonisamide, felbamate, many benzodiazepines and, to some extent, levetiracetam (Johannessen & Landmark, 2010)

- Oxcarbazepine, eslicarbazepine acetate, felbamate, rufinamide, topiramate (at doses \geq 200 mg/day) and perampanel (at doses \geq 8 mg/day) have weaker enzyme-inducing properties (Zaccara & Perucca, 2014).
- Physicians should exercise caution when withdrawing an enzyme-inducing drug from a polytherapeutic regimen, as levels of co-medications may become toxic if doses are not properly adjusted.



- Valproic acid is a broad enzyme inhibitor and can significantly increase plasma concentrations of both phenobarbital and lamotrigine. Caution should be taken when withdrawing or introducing valproic acid, as withdrawal can cause lamotrigine levels to drop, potentially causing breakthrough seizures. Conversely, when valproic acid is added to lamotrigine, serum concentrations of lamotrigine can double, increasing the risk for mild or serious rashes.
- Interactions should especially be considered for drugs with narrow therapeutic indices (i.e. carbamazepine, lamotrigine, phenobarbital, phenytoin, and valproic acid).

6.4 Therapeutic Drug Monitoring

Physicians may consider Therapeutic Drug Monitoring (TDM) in the following situations (Patsalos et al., 2008):

Please note: Decision to do TDM in a particular patient depends ultimately on the clinical judgement of the treating physician (Aícua-Rapún et al., 2020).

1. When there are uncertainties in the differential diagnosis of signs or symptoms suggestive of concentration-related ASD toxicity, or when toxicity is difficult to assess clinically (for example, in young children or in patients with mental disability).
2. When an alteration in pharmacokinetics (and, consequently, dose requirements) is suspected, due to pregnancy, liver or kidney disease, or drug-drug interactions.
3. When poor compliance by the patient is suspected.

6.5 Other Blood Tests

There is no evidence to recommend routine blood tests (blood counts and liver enzymes) either before or during ASD treatment. In special circumstances depending on the clinical situations, blood tests may be considered

(NICE, 2012; Camfield & Camfield, 2006). Examples of blood tests include:

- Before surgery (e.g. clotting studies in those on sodium valproate).
- Full blood count, electrolytes, liver enzymes, Vitamin D levels, and other tests of bone metabolism (for example, serum calcium and alkaline phosphatase) every 2–5 years for adults taking enzyme-inducing drugs (e.g. Phenytoin, Phenobarbital, Carbamazepine).
- Liver function tests when there is concern of liver injury, particularly in the presence of comorbidities or other therapies that may affect liver health.

Asymptomatic minor abnormalities in test results are not necessarily an indication for changes in medication.

6.6 Clinical Follow-up of Patients on ASD(s)

At each visit, on top of obtaining information about seizure frequency and severity, the clinician should enquire about the side effects of ASD(s).

6.7 Discontinuation of ASD(s)

There is no strong evidence in the literature to support a specific protocol for ASD withdrawal. Hence the physician may use his/her clinical judgement in deciding on ASD discontinuation on individual patients. The following suggestions may be helpful in making that decision (Beghi et al., 2013).

1. The decision to continue or withdraw medication should be taken by the patient, their family and/ or caregivers as appropriate, and the specialist after a full discussion of the risks and benefits of withdrawal. At the end of the discussion, the patient and their caregivers should understand their risk of seizure recurrence on and off treatment. This discussion should consider details of the patient's epilepsy syndrome, prognosis and lifestyle.



2. Withdrawal of ASDs must be managed by, or be under the guidance of, a pediatrician, internist or neurologist.

3. A patient with an abnormal EEG (with epileptiform discharges) at the time of treatment discontinuation should be informed of an increased risk of relapse. However, the decision to stop treatment should take into consideration the social and personal complications of seizure recurrence as well.

4. A patient with a documented structural abnormality as the etiology for his/her seizures should be informed of an increased risk of relapse.

5. Epilepsy syndrome and its natural history should be always included in the decision process at the time of treatment discontinuation.

6. When ASD treatment is being discontinued in a patient who has been seizure free, it should be carried out slowly and one drug should be withdrawn at a time. Care should be taken when withdrawing benzodiazepines and barbiturates (may take up to 6 months or longer) because of the possibility of drug-related withdrawal symptoms and/or seizure recurrence.

7. There should be a failsafe plan agreed with patients and their caregivers as appropriate, whereby if seizures recur, the last dose reduction is reversed, and medical advice is sought.

7. Patient Education and Counseling

Once a diagnosis of epilepsy is made, patients and their families will have questions concerning this diagnosis and how it will affect their lives. The lack of knowledge increases the level of felt stigma and negative attitudes about the condition (Austin, Carr, & Hermann, 2006). It is the responsibility of the health care provider to ensure that patients and their families are pro-

vided with clear, accurate and timely information about their condition and how they can access needed resources as this affects long-term adjustment to the condition (Institute of Medicine, 2012). Education and counseling needs will vary across the lifespan.

Children and adolescents:

- Managing seizures at school, common learning problems, safety, participation in extracurricular activities
- Dealing with fears (e.g.: future, death, mental health conditions, stigma)
- School and vocational planning
- Establishing healthy habits, drugs, and alcohol
- Transition to adulthood (e.g.: independence, driving, sexuality)
- Impact on family dynamics

Adults:

- Career and vocational concerns
- Discussions with employers
- Driving regulations and transportation concerns
- Sexual and gender-specific topics, such as reproductive health and family planning, hormonal changes and seizure frequency, effects of seizure medications on pregnancy
- Drug-alcohol interactions
- Impact on relationships and family dynamics
- Independent living

Seniors:

- Medication side effects, adverse interactions, and adherence
- Drug-alcohol interactions
- Independent living
- Safety and injury risks

7.2 Role of Social Worker and Community Epilepsy Agency

Epilepsy is not just a seizure disorder, but one that is known to be associated with major psychosocial challenges (Jacoby, Baker, Steen, Potts, & Chadwick, 1996).



Caregivers and patients report high satisfaction with having someone on the care team that is more accessible and who has the capacity to advocate on their behalf (Scottish Intercollegiate Guidelines Network [SIGN], 2003). Following discussion with the patient/family, referral to a social worker (where one is available) may be appropriate. The social worker can provide counseling and assist the patient/family with navigating community resources.

A Community Epilepsy Agency can:

- Provide epilepsy education and first aid training to family, friends, employers and other relevant groups.
- Provide counseling for anxiety/depression, stress management, problem-solving, self-esteem etc.
- Facilitate connections to peer supports and support groups based on needs identified.
- Advocate for patients and their families at schools, workplaces and other community agencies where they are experiencing stigma and discrimination relating to epilepsy.
- Assist patients with accessing and navigating community resources (applying for disability, respite, Trillium Drug Program etc).

Physicians caring for patients with epilepsy are encouraged to provide their patients with the contact information of their local Community Epilepsy Agency. Where there is no local agency, Epilepsy Ontario can provide this support. Contact information of the Community Epilepsy Agencies in Ontario is listed in Appendix 5.

7.3 Sudden Unexpected Death in Epilepsy (SUDEP) (updated 2020)

SUDEP is defined as sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death that occurs in benign circumstances in an individual with epilepsy,

with or without evidence for a seizure, and excludes documented status epilepticus, in which post-mortem examination does not reveal a cause of death (Devinsky, Hesdorffer, Thurman, Lhatoo & Richerson 2016). The incidence is estimated to be 1.2 cases of SUDEP per 1000 individuals with epilepsy per year (Devinsky et al., 2016).

SUDEP can occur at any age, but is most common in younger adults (aged 20–45 years). The mechanism of SUDEP is not fully understood but may involve impaired autonomic, cardiac, and respiratory function. The strongest SUDEP risk factor is poor control of primary or bilateral tonic-clonic seizures (Devinsky et al., 2016). Individuals with epilepsy may potentially reduce the risk of SUDEP by lowering seizure frequency and by adherence to anti-seizure medications (Devinsky et al., 2016).

Clinicians caring for young children with epilepsy should inform parents/guardians that in 1 year, SUDEP typically affects 1 in 4,500 children; therefore, 4,499 of 4,500 children will not be affected. Clinicians should inform adult patients with epilepsy that SUDEP typically affects 1 in 1,000 adults with epilepsy per year; therefore, annually 999 of 1,000 adults will not be affected.

For persons with epilepsy who continue to experience GTCS, clinicians should continue to actively manage epilepsy therapies to reduce seizures and SUDEP risk while incorporating patient preferences and weighing the risks and benefits of any new approach. Clinicians should inform persons with epilepsy that seizure freedom, particularly freedom from GTCS, is strongly associated with decreased SUDEP risk (Harden et al., 2017). Patients, parents and bereaved relatives prefer to have the initial discussion about SUDEP with their neurologist, and feel that this discussion should be part of the overall counseling on epilepsy. Discussions should focus on the risk and possible preventive strategies (RamachandranNair, Jack, Meaney & Ronen 2013; RamachandranNair & Jack, 2016).



7.4 Epilepsy Education Checklist

This checklist can be used by both patients and healthcare professionals to ensure that patients and their families have the information they need. Ideally, this information can be shared in a timely manner.

The information checklist may be revisited if new concerns develop (IOM, 2012). Healthcare providers may discuss the topics listed below based on their clinical judgement.

Epilepsy Information

- Definition, seizure types, syndromes, potential causes
- Explanation of medical tests
- Prognosis
- Treatment options
- Seizure diary

Medications

- Choice of anti-seizure drug
- Side effects
- Compliance
- Drug interactions
- Missed doses or suddenly stopping medications
- Medication subsidies/drug plans
- Rescue medications

First Aid

- How to assist during a seizure
- When a seizure is a medical emergency

Women and Epilepsy

- Contraception
- Preconception
- Pregnancy and breastfeeding
- Pregnancy registry
- Menopause

Lifestyle

- Diet
- Exercise
- Sleep
- Alcohol and substance abuse
- Driving regulations
- Employment
- School

Safety and Risk Factors

- Injury prevention at home and in community
- Sudden Unexpected Death in Epilepsy (SUDEP)
- Medic Alert and identification jewellery

Possible Psychosocial Consequences

- Perceived stigma
- Memory loss
- Depression
- Anxiety
- Sexual difficulties
- Low self-esteem

Community Supports

- Discussion about Community Epilepsy Agencies
- Call 1-800-463-1119 or find a list of local agencies at www.epilepsyontario.org/agency



8. Guidelines for Management of Women with Epilepsy with Special Focus on Pregnancy (updated 2020)

A management plan for women with epilepsy (WWE) should address issues related to contraception, pregnancy, and menopause. The following information outlines the basic principles of epilepsy management in WWE.

8.1 Oral Contraception

In the general population, the failure rate of oral contraception (OC) is between <1 to 7 %. Enzyme-inducing ASDs such as phenytoin (PHT), carbamazepine (CBZ), primidone (PRM), and phenobarbital (PB), as well as topiramate (TPM) (at doses higher than 200 mg/day) and oxcarbazepine (OXC) may increase the failure rate of OC. CBZ decreases levels of contraceptive steroids, increases breakthrough bleeding and does not adequately protect women from pregnancy (Davis et al., 2001).

There is evidence that oral contraception may reduce levels of lamotrigine (LTG). Intrauterine devices do not appear to interact with ASDs.

Recommendations:

1. Enzyme-inducing ASDs should be avoided (if possible) in women with epilepsy who are using oral contraceptives, transdermal patches, or levonorgestrel implants.

8.2 Pregnancy

Although most women with epilepsy have healthy pregnancies, there is an increased risk of complications associated with ASD treatment as well as seizure recurrence. These risks involve the mother (patient) as well as the embryo/fetus.

Pregnancy increases the clearance of most ASDs and is associated with a decrease in drug levels, particularly for LTG, CBZ, and PHT. Exposure to ASDs during pregnancy is associated with an increased risk of congenital malformations, and may have an adverse effect on fetal growth and psychomotor development.

Unplanned pregnancies are common in WWE, and preconceptual counselling in this population is recommended. (NICE 2012; Harden et al., 2009a, 2009c)

- WWE who are seizure-free for at least 9 months prior to pregnancy have a high likelihood (84-92%) of remaining seizure-free during pregnancy. ASD levels may decline during pregnancy due to changes in the volume of distribution. This is particularly seen with LTG and PHT.

- Preconceptional folate decreases the risk of midline birth defects and low IQs in the offspring of WWE. Based on a practice guideline published by the American Academy of Neurology, the recommended dose may be between 0.4 mg/d to 4 mg/d, but due to the weak evidence in the literature, the optimal dose of folic acid needs to be determined.

- Generalized tonic-clonic seizures may result in more profound hypoxia than in the non-gravid state due to increased maternal oxygen requirements. This may have adverse effects for the fetus.

- There is no evidence that focal, absence and myoclonic seizures adversely affect the pregnancy or developing fetus.

- Genetic counselling should be considered if one partner has epilepsy, particularly if the partner has genetic epilepsy or a positive family history of epilepsy.

- There is some evidence of increased risk of premature contractions and premature labor and delivery in WWE who smoke.

- There is no strong evidence of an increased risk of caesarean delivery in WWE taking ASDs.

8.3 Placental Transfer and Teratogenicity

ASDs readily cross the placenta from the mother into the fetus.



PB, PRM, PHT, CBZ, levetiracetam (LEV) and valproic acid (VPA) likely cross the placenta in potentially clinically important amounts, while gabapentin (GBP), lamotrigine (LTG), OXC and TPM possibly cross the placenta in potentially clinically important amounts (Harden et al., 2009b). Despite extensive passage, there is no evidence to link level of exposure to adverse neonatal outcomes. Evidence suggests that the adverse neurodevelopmental effects of a medication likely outweigh the amount of drug exposure (Bank et al., 2017).

- Exposure to VPA is associated with midline birth defects including spina bifida (6-10%), autism-spectrum disorder, as well as lower verbal IQ in children of mothers exposed to ASDs during pregnancy (see section 6.4) . Women taking VPA who are thinking of becoming pregnant should change to another ASD, if possible, well before pregnancy as the risk of major congenital malformations (MCMs) occurs very early in pregnancy.
- Exposure to CBZ is associated with an increased risk of malformations but to a lesser extent than VPA. The risk with PB appears to be related specifically to cardiac malformations in comparison to other ASDs. There is some evidence that pregabalin may confer a higher risk of MCMs (Winterfeld et al., 2016), but further research is required.
- There appears to be an associated risk of facial clefts with Topiramate (Hunt et al., 2008; Margulis et al., 2012).
- Offspring of women with epilepsy taking ASDs have a higher risk of having a small for gestational age birthweight and having a one-minute Apgar score of <7 (Harden et al., 2009b).
- There is increased risk of birth defects with ASD polytherapy (when compared with monotherapy).
- Based on current evidence, LEV and LTG exposure carry the lowest risk of overall mal-

formation; however, data pertaining to specific malformations are lacking (Weston et al., 2016).

- Enzyme-inducing ASDs are thought to competitively inhibit the precursors of Vitamin K-dependent clotting factors and alter fetal vitamin K metabolism. However, there is insufficient evidence to determine if the risk of neonatal hemorrhagic complications in the newborns of WWE taking ASD are substantially increased (Harden et al., 2009c).

8.4 Valproic Acid

Valproic acid (VPA) is a known teratogen, and prenatal exposure is linked to a threefold increase in the risk of MCMs, including spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis. This prevalence of MCMs in children exposed to VPA is 10.93%, and the risk of MCMs is 2-7 x greater than with other widely used ASDs (Weston et al., 2016). The teratogenic effects are dose-dependent and greatest at daily doses >1000 mg/day.

VPA is now also recognized as a neurobehavioural teratogen (Weston et al., 2016), and exposure in utero is associated with an increased risk of a range of neurodevelopmental deficits, including poorer school performance, lower IQ in school aged children, and an increased risk of autism spectrum disorders (Tomson et al., 2016; Elkjær et al., 2018).

Poorer neurodevelopmental outcomes for children exposed to VPA is consistently reported, with a mean reduction of 8 to 10 IQ points, which may affect cognitive, educational and occupational outcomes later in life (Bromley et al., 2014). Similarly, higher doses (800 to 1000 mg daily or above) are associated with a poorer cognitive outcome in the child (Bromley et al., 2014).

Recommendations: (NICE 2012; Tomson et al., 2015; Tomson et al., 2016)



1. Whenever possible, VPA should be avoided in women of childbearing potential.
2. WWE taking VPA should be counselled on the risks of malformations and possible neurodevelopmental impairments in an unborn child and given information about alternative ASDs.
3. Physicians should specifically discuss the risk of continued use of VPA to the unborn child, being aware that higher doses of VPA (more than 800 mg/day) and polytherapy, particularly VPA, are associated with greater risk.
4. Both teratogenicity and efficacy need to be considered. Risks and benefits need to be carefully weighed in women with generalized epilepsies, such as juvenile myoclonic epilepsies, for which VPA has the best evidence of efficacy.
5. When used in women of childbearing potential, VPA should be prescribed at the lowest effective dose, when possible aiming at doses not exceeding 500-600 mg/day.
6. For women on VPA who are already pregnant, withdrawal can be considered if risks are acceptable and if VPA is not needed to maintain seizure control.

8.5 Breastfeeding

Although the total amount is less than is transferred via the placenta, breastfeeding may lead to drug accumulation in infants. Primidone and levetiracetam likely penetrate into breast milk in potentially clinically significant amounts. Gabapentin, lamotrigine and topiramate possibly penetrate into breast milk, while valproic acid, phenobarbital, phenytoin and carbamazepine probably do not (Harden et al., 2009c). Breast milk concentrations of barbiturates, benzodiazepines, lamotrigine, zonisamide and ethosuximide may be elevated, and women should be advised to monitor infants for side effects such as lethargy, irritability and sedation (Stephen et al., 2019). However, there is insufficient evidence to link ASDs

ingested through breast milk to clinically significant outcomes (Harden et al., 2009c), and breastfeeding has beneficial effects for both mother and child. Thus, breastfeeding for most women and girls taking ASDs is generally safe and not contraindicated in women with epilepsy.

General Recommendations for WWE who are pregnant or considering pregnancy:

1. Treating physician should aim for seizure freedom prior to pregnancy.
2. Simplify regimen to monotherapy at the lowest dose, if possible.
3. Women and girls with generalized tonic-clonic seizures should be informed that the fetus may be at relatively higher risk of harm during a seizure, although the absolute risk remains very low, and the level of risk may depend on seizure frequency (NICE, 2012).
4. The possibility of status epilepticus and SUDEP should be discussed with all women and girls who plan to stop ASD therapy (NICE, 2012).
5. Discuss with women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years), and their parents and/or caregivers if appropriate, the risk of ASDs causing malformations and possible neurodevelopmental impairments in an unborn child. Assess the risks and benefits of treatment with individual drugs. There are limited data on risks to the unborn child associated with newer drugs. Specifically discuss the risk of continued use of VPA to the unborn child, being aware that higher doses (more than 800 mg/day) and polytherapy, particularly with VPA, are associated with greater risk (NICE 2012).
6. Determine ASD levels during each trimester of pregnancy. If possible, obtain two serum concentration levels before pregnancy when the seizures are well controlled. This can be used as a reference range during pregnancy.



More frequent monitoring is suggested if the patient has difficulty to control seizures or is sensitive to change in dose/concentrations, and with Lamotrigine or Oxcarbazepine (Patsalos et al., 2008).

7. Use of folic acid (0.4 - 4 mg/day) is highly recommended, starting pre-conceptionally.
8. Monitor closely for obstetrical complications.
9. Encourage smoking cessation in WWE.
10. Use of Vitamin K prior to delivery is not routinely indicated.
11. Breastfeeding is not contraindicated.

8.6 Menopause

Increased rates of early menopause have been observed in WWE, with age of onset negatively correlated with seizure frequency (Shifren & Gass, 2014). In addition, the use of hormone replacement therapy may be associated with an increase in seizure frequency (Harden et al., 2006). Women who are menopausal and taking enzyme-inducing ASDs may be at greater risk of bone fractures (Brodie et al., 2013; Fraser et al., 2015) and should undergo regular screening for osteoporosis.

Recommendations:

1. If possible, enzyme-inducing ASDs should be avoided in women at risk for osteoporosis.
2. The use of daily Vitamin D and calcium supplements is recommended in menopausal women.
3. Women taking enzyme-inducing ASDs should undergo regular screening for osteoporosis.
4. Hormone replacement therapy should be used with caution, as it may increase seizure frequency.

9.0 Guidelines on Referring Patients

9.1 From the Emergency Department

- Patients with new-onset epileptic seizure(s) should be advised to follow up with their General Practitioner (GP) or Family Physician (FP). If the patient has no GP/FP, referral to a pediatrician/ internist (depending on the age of the patient) or neurologist should be made.
- Availability, geographic proximity, and wait time should be considered when choosing the appropriate specialist. Some hospitals have first seizure clinics run by neurologists.
- ED physicians should facilitate an outpatient EEG requisition if a follow up plan has been arranged with the appropriate specialist.
- Patients with an established diagnosis of epilepsy may present to the ED after recurrence of seizures. These patients should be advised to follow up with their GP/FP or specialist.

9.2 From General Practitioner/Family Physician

- After the first unprovoked epileptic seizure, patients should be referred for an EEG, and imaging of the brain, preferable MRI, with the exception of the genetic generalized epilepsies (e.g. JME, childhood absence epilepsy). Patients with abnormalities in the MRI should be referred to a specialist. Availability, geographic proximity, and wait time should be considered when choosing the appropriate specialist.
- Once the diagnosis of epilepsy is established, treatment with ASD may be initiated by the GP/FP if the physician is comfortable in initiating it. Otherwise, the patient should be referred to a specialist.



- All patients who fail to respond to adequate trial of the first ASD should be referred to a neurologist. If the first ASD is withdrawn due to side effects, it may not necessarily be concluded that the threshold for adequate trial with the first ASD was reached.

9.3 From Pediatricians/Internist

- Appropriate investigations (e.g. EEG and if needed MRI) should be arranged before referring the patient to a neurologist.
- All patients who fail to respond to an adequate trial of the first ASD should be referred to a neurologist. If the first ASD is withdrawn due to side effects, it may not necessarily be concluded that the threshold for adequate trial with the first ASD was reached.

9.4 Referring Patients to Epileptologists

Currently in Ontario there is a delay from time of diagnosis to time of surgery in those who have surgically remediable epilepsy. The longer the medically refractory epilepsy goes on, the worse the psychosocial and cognitive outcomes are. Therefore, any patient, adult or child, with medically refractory focal seizures is a surgical candidate until proven otherwise. All patients in Ontario with medically refractory focal seizures should be referred to an epileptologist in a District Epilepsy Centre in order to assess surgical candidacy, sooner rather than later.

More specific indications for referral to an epileptologist are mentioned below:

9.4.1 Adult Patients

- All patients with medically refractory epilepsy
- Patients requiring prolonged Video-EEG Monitoring in the EMU.
- Patients with epilepsy can be referred to an epileptologist by a physician based on his/her clinical judgment, even if the epilepsy is not medically refractory.

9.4.2 Pediatric Patients

- All patients who are potential surgical candidates
- All patients who require diet therapy for epilepsy
- If geographical proximity is not an issue, all patients with medically refractory epilepsy should be evaluated by an epileptologist at least once to ensure diagnostic accuracy, appropriate work up, correct medications, and to determine surgical candidacy. If this is not practical, an attempt should be made to obtain telephone consultation (with on-going communication) with the epileptologist.
- Patients with epilepsy can be referred to an epileptologist by a physician based on his/her clinical judgment, even if the epilepsy is not medically refractory.

9.5 Model for Co-management

9.5.1 Co-management of patients by GP/FP and the neurologist:

Patients who do not need to be followed by the neurologist after the initial consultation are followed by the GP/FP for implementing the neurologist's recommendations, prescription renewal and follow up assessment as outlined in the 'Guidelines on Follow-Up' below. GP/FP may request re-assessment by the neurologist, if needed.

9.5.2 Co-management of patients by pediatrician/internist and the neurologist:

Patients who do not need to be followed by the neurologist after the initial consultation are followed by the internist/pediatrician for implementing the neurologist's recommendations, prescription renewal and follow up assessment as outlined in the 'Guidelines on Follow-Up' below. Pediatrician/internist may request re-assessment by the neurologist, if needed.



9.5.3 Co-management by Nurse Practitioners (NPs):

In a primary care setting, NPs play a vital role in co-managing patients with epilepsy. It is recommended that NPs initiate the first ASD only in consultation with the GP/ FP. EEG and MRI brain are requested by the GP/FP as outlined in this document. After the initial specialist consultation, those who do not need to be followed by the specialist on a regular basis may be followed by the NPs for implementing the specialist's recommendations, prescription renewal within the scope of practice and follow up assessment as outlined in the 'guideline on follow up' below.

In a hospital setting where a NP is part of a healthcare team that includes a specialist, a co-management model with the specialist should be developed where the role of NP is clearly outlined. All ASD management should be performed under the supervision of the specialist.

10. Guidelines on Follow-up

10.1 Patients Without Prolonged Seizure-Free Period

During follow up, enquiry should be made regarding new seizure types, efficacy and side effects of ASDs, and in children, impact on growth and development. Based on new clinical information including results of investigation(s), diagnosis and management plan may have to be changed.

In the first year of life, infants should be seen every 3 months for assessment of their growth and development for the following reasons:

- To assess the neurodevelopmental progress
- To adjust their medication dose for growth, if required

Toddlers and children aged 1-12 years should

be reviewed every 3-6 months for the following reasons:

- To assess the developmental progress
- To discuss the school performance
- To discuss risks of seizures while engaged in water sports, bathing etc.

Teenagers aged 13-17 years can be reviewed every 6-12 months:

- To readjust medication need at the onset of puberty, if required
- To discuss the effect of alcohol on epilepsy threshold
- To discuss pregnancy planning need in teenage girls with epilepsy
- To discuss driving laws as applicable to epilepsy
- To discuss transition to adult care

Adults with epilepsy can be reviewed every 3-6 months:

- To adjust medication for side effects/ poor seizure control
- To assess for psychiatric (depression, anxiety) and physical (osteoporosis, dyslipidemia) comorbidities
- To assess social adjustment and offer counseling
- To review seizure control and medication adjustments during pregnancy

At all ages, patients with breakthrough seizures should have access to epilepsy care and communication with their treating physician/NP for advice on seizure management and assessment of medication compliance. Support from social worker, clinical psychology and/or community agency may be considered at any time.



10.2 Patients After Prolonged Seizure-Free Interval

In general, patients who have been seizure free for 2 years or more should be reassessed for the need for continuation or discontinuation of ASDs.

11. Guidelines on Comorbidities

11.1 Major comorbidities

Comorbidity 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.

Relevance to Epilepsy:

Comorbid conditions are common in people with epilepsy, and their presence has important implications for diagnosis, treatment, medical costs and quality of life. Comorbid conditions in epilepsy are found across the lifespan, and include medical, psychiatric and cognitive conditions alone or in combination.

Comorbid conditions with significantly higher rates in patients with epilepsy than the general population:

Medical:

- Musculoskeletal system disorders
- Gastrointestinal and digestive disorders
- Respiratory system disorders
- Chronic pain disorders
- Cerebrovascular accidents
- Migraine
- Neoplasia
- Arthritis/rheumatism
- Obesity
- Diabetes
- Infections
- Fractures
- Allergies
- Alcoholism
- Drug abuse

Psychiatric:

- Depression
- Anxiety
- Autism spectrum disorders
- Interictal dysphoric disorder
- Interictal behavior syndrome
- Psychosis of epilepsy

Cognitive:

- Attention-deficit hyperactivity disorder
- Learning disability
- Intellectual Development Disorder
- Alzheimer's disease/dementia

11.2 Depression (updated 2020)

Depression is increased in people with epilepsy, with a lifetime prevalence of about 30% (Tellez- Zenteno, Patten, Jette, Williams, & Wiebe, 2007). Seizure focus may be a determinant, but psychosocial factors such as life stress, coping style, social support, perceived stigma and personality are more consistent predictors of depression in PWE (Maguire et al., 2014).

Case-control studies have shown that patients with depression have a two- to seven-fold higher risk of developing epilepsy. Potential mechanisms include shared pathology, structural lesions or genetic susceptibility. However, it is also possible that antidepressant use may trigger seizures (Maguire et al., 2014). Clinicians should be aware that depression and even suicidal ideation can be adverse effects of ASDs. The rate of suicidal ideation was reported to be 23.2% among PWE, considerably higher than the general population (Abraham et al., 2019).

Despite the frequency and significance of depression in persons with epilepsy, it remains underdiagnosed and undertreated (Barry, Ettinger, & Friel, 2008). Depression has a significant negative impact on quality of life. In contrast to many other neurological conditions, social stigma and public ignorance represent a specific additional burden of epilepsy (Hoppe & Elger, 2011).



There is concern that patients may not be receiving appropriate treatment for their depression because of uncertainty regarding which antidepressant or class works best and the perceived risk of exacerbating seizures.

Screening for depression using the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), Patient Health Questionnaire (PHQ-2), or an equivalent tool should ideally be undertaken for all patients (adults and adolescents aged 13-17 years) with epilepsy by their primary care physicians or specialists. This screening should be conducted soon after the diagnosis, and thereafter on an annual basis (Kerr et al., 2011). However, many experts recommend more frequent screening as depression-associated symptoms and suicidal ideation may occur at any time during the disease course (Fecske et al., 2020).

In those diagnosed with depression, treatment should be considered or referral to a mental health specialist. Anti-depressant drugs of the selective serotonin reuptake inhibitor (SSRI) or selective norepinephrine reuptake inhibitor (SNRI) families are the first line of therapy in depressive disorders, and the use of antidepressant drugs is safe in patients with epilepsy when used at therapeutic doses (Kanner, 2013). However, amoxapine, bupropion, clomipramine and maprotiline may demonstrate proconvulsant effects at therapeutic doses and should be avoided (Kanner, 2016). Non-pharmacological approaches such as cognitive behavioural therapy may also be appropriate (Dobson, 1989).

Recommendations: (Kerr et al., 2011; Mula et al., 2013; Kanner, 2016; ILAE 2019)

1. At minimum, annual screening for depression is recommended, but more frequent screening may be useful as depression can be episodic.
2. When starting an ASD or switching from one to other ASDs, patients should be advised to report any changes in mood and suicidal ideation to their treating physician.
3. The Columbia Suicide Severity Rating Scale (C-SSRS) represents a suitable and reliable instrument to evaluate suicidality.
4. Neurologists, epileptologists, or internists with training/skills in treating depression can, after diagnosing an episode of depression, start antidepressant therapy if interictal depression is identified.
5. Treatment options include cognitive behavioural therapy/psychotherapy and antidepressants. SSRIs, where available, should be considered as first-line pharmacologic treatment as they have a low seizure propensity and favorable side-effect profile. However, prescribers should be aware of the possible enzyme-inhibiting effects of SSRIs such as fluoxetine and fluvoxamine, which may lead to increases in ASD levels. Additionally, co-medication with enzyme-inducing ASDs can increase the clearance of antidepressant drugs.
6. Antidepressant use in PWE is generally safe; however, amoxapine, bupropion, clomipramine and maprotiline should be avoided.
7. Continue antidepressant therapy for 6 months after recovery from the first depressive episode and continue for at least 2 years after recovery from a second and/or subsequent episode(s).
8. Be aware that withdrawal of ASDs that have positive psychotropic effects can lead to depression; therefore, reintroduce the implicated ASD (when indicated) to ameliorate depressive symptoms.
9. All PWE diagnosed with depression should, in addition to antidepressants, be offered nonpharmacologic interventions, unless the depression is in such a severe phase that they could not benefit.



10. Supportive therapy, including psychoeducation provided by trained therapists, social workers, epilepsy nurse specialists, or other suitably trained professionals, should be provided to all newly diagnosed PWE and their families. Families that receive education on the importance of mental health and risk of depression have improved attitudes toward mental health.

11.3 Anxiety

The prevalence of various forms of anxiety is very high among persons with epilepsy, ranging from 19-60% (Jones et al., 2005). Panic disorder, generalized anxiety disorder, phobias and obsessive-compulsive disorders are all increased in persons with epilepsy (Beyenburg et al., 2005). Focal epilepsies of temporal lobe origin have a stronger association than other seizure types. The effects of anxiety on quality of life are substantial and separate from the effects of depression (Cramer, Brandenburg, & Xu, 2005).

Patients with epilepsy should be screened for symptoms of anxiety. Anxiety disorders commonly co-occur with mood disorders in PWE. The NDDI-E screens for both depression and anxiety. The diagnosis and management of anxiety disorders should be incorporated into the patient's treatment plan. Patients should be referred to neuropsychiatry/psychiatry or a clinical psychologist, as appropriate.

Please see Appendix 5 for a list and description of some of the co-morbidities associated with epilepsy other than anxiety and depression.

11.4 Stigma

Stigma remains a significant source of stress and limitations for PWE (Hermann et al., 2016), and is experienced in two main ways: felt (or internalized) stigma refers to the shame of having seizures and the fear of encountering epilepsy-linked enacted stigma, while enacted (or institutionalized) stigma reflects actions of discrimination that people with epilepsy face in

their communities (World Health Organization, 2019). Stigma is highly associated with seizure frequency and is linked to poor psychosocial outcomes, including depression, anxiety and social isolation (Bandstra, Camfield & Camfield, 2008). Higher perceived epilepsy-related stigma is associated with lower medication adherence, low quality of life, a reduced sense of self-efficacy and poorer health-related outcomes (Baker, Eccles & Caswell, 2018).

Evidence strongly suggests those who are better informed about their epilepsy are less likely to feel stigmatized, and thus targeted educational programs and counseling for people with epilepsy and their families are clearly indicated (Baker 2002; de Boer, Mula & Sander, 2008). Stigma reduction measures should be culturally appropriate, education-focused and patient-centred and should convey positive messages (England et al., 2012). Support and self-help groups, where participants can exchange ideas and learn coping strategies through peer support, can be empowering for people with epilepsy (World Health Organization, [WHO] 2019).

Recommendations (NICE, 2004; WHO, 2019):

1. Health care providers have a responsibility to educate others about epilepsy so as to reduce the stigma associated with it. They should provide information about epilepsy to all people who come into contact with children, young people and adults with epilepsy, including school staff, social care professionals and others.
2. Health care providers and Community Epilepsy Agencies can support PWE by providing information to improve health literacy and to help individuals and families cope with the fear of living with the unpredictability of seizures, learn more about their diagnosis, and ways to disclose their epilepsy to others.
3. Stigma training can help health care providers to better understand the psychosocial impact of epilepsy on patients and families.



References

- Abraham, N., Buvanawari, P., Rathakrishnan, R., Tran, B.X., Thu, G.V., Nguyen, L.H., Ho, C.S., & Ho, R.C. (2019). A Meta-Analysis of the Rates of Suicide Ideation, Attempts and Deaths in People with Epilepsy. *International Journal of Environmental Research and Public Health*, 24;16(8).
- Abou-Khalil, B.W. (2019). Update on Antiepileptic Drugs. *Continuum* (Minneapolis, Minn); 25(2):508-536.
- Aícuá-Rapún, I., André, P., Rossetti, A.O., Ryvlin, P., Hottinger, A.F., Decosterd, L.A., Buclin, T., & Novy, J. (2020). Therapeutic Drug Monitoring of Newer Antiepileptic Drugs: A Randomized Trial for Dosage Adjustment. *Annals of Neurology*; 87(1):22-29.
- Arntz, R.M., Noortje, A.M., Maaijwee, Loes CA Rutten-Jacobs, Hennie C. Scheonderwaldt, Lucille D. Dorresteyn, Ewoud J. van Dijk, and Frank-Erik de Leeuw. (2013). Epilepsy after TIA or stroke in young patients impairs long-term functional outcome The FUTURE Study. *Neurology*, 81, no. 22 1907-1913.
- Austin, J. K., Carr, D.A., & Hermann, B.P. (2006). Living well II: A review of progress since 2003. *Epilepsy & Behavior*, 9, Issue 3: Pages 386-393.
- Baker, G. (2002). People with epilepsy: what do they know and understand, and how does this contribute to their perceived level of stigma? *Epilepsy & Behavior* 3: S26-S32
- Baker, D., Eccles, F.J.R., Caswell, H.L. (2018). Correlates of stigma in adults with epilepsy: a systematic review of quantitative studies. *Epilepsy & Behavior*; 83:67-80
- Bandstra, N.F., Camfield, C.S., & Camfield, P.R. (2008) Stigma of epilepsy. *Canadian Journal of Neurological Sciences*; 35(4):436-40.
- Bank, A.M., Stowe, Z.N., Newport, D.J., Ritchie, J.C., & Pennell, P.B. (2017) Placental passage of antiepileptic drugs at delivery and neonatal outcomes. *Epilepsia* 58(5):e82-e86.
- Barry, J.J., Ettinger, A.B., Friel, P., et al. (2008). Consensus statement: the evaluation and treatment of people with epilepsy and affective disorders. *Epilepsy & Behaviour*, 13, S1-29.
- Beghi, E., Giussani, G., Grosso, S., Iudice, A., La Neve, A., Pisani, F., & Specchio L. M et al. (2013). Withdrawal of antiepileptic drugs: Guidelines of the Italian League Against Epilepsy. *Epilepsia*, 54, no. s7: 2-12.
- Berg, A.T., Berkovic, S. F., Brodie, M. J., Buchhalter, J., Cross, H. J., Van Emde Boas, W., & Engel, J., et al. (2010). Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia*, 51, no. 4: 676-685.
- Berg, A.T. (2008). Risk of recurrence after a first unprovoked seizure. *Epilepsia*, 49, no. s1: 13-18.
- Bergey, G.K. (2004). Initial treatment of epilepsy: Special issues in treating the elderly. *Neurology* 63, no. 10 suppl 4: S40-S48.
- Beyenburg, S., Mitchell, A. J., Schmidt, D., Elgar, E., & Reuber, M. (2005). Anxiety in patients with epilepsy: systematic review and suggestions for clinical management. *Epilepsy & Behavior*, 7, no. 2: 161-171.
- Bhatt, H., Matharu, M. S, Henderson, K. & Greenwood, R. (2005). An audit of first seizures presenting to an Accident and Emergency department. *Seizure*, 14, no. 1: 58-61.
- Biton, V. (2006). Weight change and antiepileptic drugs: health issues and criteria for appropriate selection of an antiepileptic agent. *The Neurologist*, 12, no. 3: 163-167.
- Bleck, T. P. (2012). Seven Question About Stroke and Epilepsy. *Epilepsy Currents*, 12(6), 225-228.
- Bompaire, F., Barthelemy, S., Monin, J., Quirins, M., Marion, L., Smith, C., Boulogne, S., & Auxemery, Y. (2019) PNES Epidemiology: what is known, what is new? *European Journal of Trauma & Dissociation* Available online 22 October 2019, 100136. In Press, Journal Pre-proof
- Bowen, J.M., Snead, O.C., Chandra, K., Blackhouse, G., & Goeree, R. (2012). Epilepsy care in Ontario: an economic analysis of increasing access to epilepsy surgery. *Ontario Health Technology Assessment Series*, 12, 1-41.
- Bowley, C. & Kerr, M. (2000). Epilepsy and intellectual disability. *Journal of Intellectual Disability Research*, 44, 529-543.
- Bromley, R., Weston, J., Adab, N., Greenhalgh, J., Sanniti, A., McKay, A.J., Tudur Smith, C., & Marson, A.G. (2014) Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. *Cochrane Database of Systematic Reviews*, Issue 10. Art. No.: CD010236.
- Brown, M.G., Becker, D.A., Pollard, J.R., Anderson, C.T. (2013). The diagnosis and treatment of attention deficit hyperactivity disorder in patients with epilepsy. *Current Neurology and Neuroscience Reports*, 13, 13:351.
- Burneo, J.G., Shariff, S.Z., Liu, K., Leonard, S., Saposnik, G., & Garg, A.X. (2016) Disparities in surgery among patients with intractable epilepsy in a universal health system. *Neurology* 86(1):72-8.
- Camfield, P., & Camfield, C. (2006). Monitoring for adverse effects of antiepileptic drugs. *Epilepsia*, 47, no. s1: 31-34.
- Canadian Society of Clinical Neurophysiologists (2002). Minimal Standards for Electroencephalography in Canada. *Canadian Journal of Neurological Sciences*, 29, 216-220.



References

- Carlson, P. & Nicholson Perry, K. (2017). Psychological interventions for psychogenic non-epileptic seizures: A meta-analysis. *Seizure*; 45:142-150.
- Chambers, C., Jansen, L. A., & Dhamija, R. (2016). Review of Commercially Available Epilepsy Genetic Panels. *Journal of Genetic Counseling*, 25(2), 213-217.
- Chaves, J. & Sander J.W. (2005) Seizure aggravation in idiopathic generalized epilepsies. *Epilepsia*, 46, Suppl 9:133-9.
- College of Emergency Medicine (CEM) (2009). Laboratory investigations and bedside tests. Guideline for the Management of First Seizure in the Emergency Department. *Guidelines in Emergency Medicine Network (GEMNet)*. Retrieved from: <https://secure.collemergencymed.ac.uk/code/document.asp?ID=5073>
- Cramer, J.A., Brandenburg, N., & Xu, X. (2005). Differentiating anxiety and depression symptoms in patients with partial epilepsy. *Epilepsy & Behavior*, 6(4):563-9.
- Dalrymple, J., & Appleby, J. (2000). Cross sectional study of reporting of epileptic seizures to general practitioners. *British Medical Journal*, 320, no. 7227: 94-97.
- Daniels, Z. S., Nick, T.G., Liu, C., Cassidy, A. & Glauser, T.A. (2009). Obesity is a common comorbidity for pediatric patients with untreated, newly diagnosed epilepsy. *Neurology* 73, no. 9: 658-664.
- Dash, D., Dash, C., Primrose, S., Hernandez-Ronquillo, L., Moien-Afshari, F., Ladino, L.D., Appendino, J.P., Mazepa, L., Elliott, C., Mirsattari, S.M., Federico, P., Bui, E., Hunter, G., RamachandranNair, R., Sharma, R., Melendres, P., Nikkel, J., Nguyen, D.K., Almubarak, S., Rigby, M., & Téllez-Zenteno, J.F. (2017) Update on Minimal Standards for Electroencephalography in Canada: A Review by the Canadian Society of Clinical Neurophysiologists. *Canadian Journal of Neurological Sciences*; 44(6):631-642.
- Dashti, H.M., Mathew T.C., Hussein, T., Asfar, S.K., Behbahani, A., Khoursheed, M.A., Al-Sayer, H. M., Bo-Abbas, Y.Y., & Al-Zaid, N.S. (2004). Long-term effects of a ketogenic diet in obese patients. *Experimental & Clinical Cardiology* 9, no. 3: 200.
- Davis, A.R., Westhoff, C.L., & Stanczyk, F. Z. (2011). Carbamazepine coadministration with an oral contraceptive: effects on steroid pharmacokinetics, ovulation, and bleeding. *Epilepsia* 52, no. 2: 243-247.
- de Boer, H.M., Mula, M., Sander, J.W. (2008) The global burden and stigma of epilepsy. *Epilepsy & Behavior*; 12(4):540-6.
- Devinsky, O., Gazzola, D., & LaFrance, W.C. Jr. (2011) Differentiating between nonepileptic and epileptic seizures. *Nature Reviews Neurology*; 7(4):210-20.
- Devinsky, O., Hesdorffer, D.C., Thurman, D.J., Lhatoo, S., Richerson, G. (2016) Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. *Lancet Neurology* 15(10):1075-88.
- Dobson, K.S. (1989). A meta-analysis of the efficacy of cognitive therapy for depression. *Journal of Consulting and Clinical Psychology*, 57, 414-9.
- Donner, E.J. & Snead III, O.C. (2006). New generation anticonvulsants for the treatment of epilepsy in children. *NeuroRX*, 3, no. 2: 170-180.
- Dreifuss, F.E., Santilli, N., Langer, D.H., Sweeney, K.P., Moline, K. A. & Menander, K. B. (1987). Valproic acid hepatic fatalities: A retrospective review. *Neurology*, 37, no. 3: 379-379.
- Dyment, D.A., Prasad, A.N., Boycott, K.M., Ediae, G.U., Hartley, T., Hassan, A., Muir, K.E., Potter, M., Boisse Lomax, L., Jarinova, O., Sadikovic, B., Stavropoulos, D.J., Snead, O.C. (2019). Implementation of epilepsy multigene panel testing in Ontario, Canada. *Canadian Journal of Neurological Sciences*; 7:1-8
- Elkjær, L.S., Bech, B.H., Sun, Y., Laursen, T.M., & Christensen, J. (2018) Association Between Prenatal Valproate Exposure and Performance on Standardized Language and Mathematics Tests in School-aged Children. *JAMA Neurology* 1;75(6):663-671.
- England, M.J., Liverman, C.T., Schultz, A.M., Strawbridge, L.M. (2012) Epilepsy across the spectrum: promoting health and understanding. A summary of the Institute of Medicine report. *Epilepsy & Behavior*; 25(2):266-76.
- Epilepsy: a public health imperative. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO. European Handbook of Neurological Management: Volume 1, 2nd Edition - Edited by N. E. Gilhus, M. P. Barnes and M. Brainin © 2011 Blackwell Publishing Ltd. ISBN: 978-1-405-18533-2 Chapter 29 Alcohol - related seizures.
- Fecske, E., Glasier, P., Vargas Collado, L.M., & Rende, E. (2020). Standardized Screening for Depression in Pediatric Epilepsy. *Journal of Pediatric Health Care*; 34(1):47-53.
- Ferrie, C.D. (2006). Preventing misdiagnosis of epilepsy. *Archives of disease in childhood*, 91(3), 206-209.
- Filipek, P. A., Accardo, P. J., Ashwal, S., Baranek, G.T., Cook, E.H., Dawson, G., & Gordon, B. et al. (2000). Practice parameter: Screening and diagnosis of autism. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society. *Neurology* 55, no. 4: 468-479.



References

- Fisher, R.S., Boas, E.V., Blume W., Elger C., Genton, P., Lee, P., & J. Engel. (2005) Epileptic Seizures and Epilepsy: Definitions Proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia*, 46, 470– 472.
- Fisher, R.S., Acevedo, C, Arzimanoglou, A, Bogacz, A, Cross J.H., Elger CE, Engel J Jr, Forsgren L, French J.A., Glynn M, Hesdorffer D.C., Lee B.I., Mathern G.W., Moshé, S.L., Perucca, E., Scheffer, I.E., Tomson, T., Watanabe, M., & Wiebe, S. (2014). ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*, 55(4):475-82.
- Fraser, L.A., Burneo, J.G., & Fraser, J.A. (2015) Enzyme-inducing antiepileptic drugs and fractures in people with epilepsy: A systematic review. *Epilepsy Research*. 116:59-66. Gaillard, W.D., Chiron, C., Cross, J.H., Kuzniecky, R., Hertz-Pannier, L., & Vezina, L.G. (2009) Guidelines for imaging infants and children with recent-onset epilepsy. *Epilepsia*, 50(9):2147-53.
- Gayatri, N.A. & Livingston, J.H. (2006). Aggravation of epilepsy by anti-epileptic drugs. *Developmental Medicine Child Neurology*, 48(5):394-8.
- Glauser, T., Ben-Menachem, E., Bourgeois, B., Cnaan, A., Guerreiro, C., Kälviäinen, R., Mattson, R., French, J.A., Perucca, & E., Tomson, T. (2013) ILAE Subcommission on AED Guidelines. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia*, 54(3):551-63. doi: 10.1111/epi.12074.
- Glauser, T., Ben Menachem, E., Bourgeois, B., Cnaan, A., Chadwick, D., Guerreiro, C., Kalviainen, R., Mattson, R., Perucca, E. & Tomson, T. (2006). ILAE Treatment Guidelines: Evidence-based Analysis of Antiepileptic Drug Efficacy and Effectiveness as Initial Monotherapy for Epileptic Seizures and Syndromes. *Epilepsia* 47, no. 7 : 1094-1120.
- Grover, S. & Kukreti, R. (2014). HLA alleles and hypersensitivity to carbamazepine: an updated systematic review with meta- analysis. *Pharmacogenetics and genomics* 24, no. 2 : 94-112.
- Guerrini, R., Belmonte, A., Genton, P. (1998). Antiepileptic drug-induced worsening of seizures in children. *Epilepsia*, 39, Suppl 3:S2-10.
- Harden, C.L., Herzog, A.G., Nikolov, B.G., Koppel, B.S., Christos, P.J., Fowler, K., Labar, D.R., & Hauser, W.A. (2006). Hormone replacement therapy in women with epilepsy: a randomized, double-blind, placebo-controlled study *Epilepsia*; 47(9):1447-51.
- Harden, C.L., Hopp, J, Ting, T.Y., Pennell, P.B., French, J.A., Hauser, W.A., et al. (2009a). Practice parameter update: management issues for women with epilepsy - focus on pregnancy (an evidence-based review): obstetrical complications and change in seizure frequency report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology* 73(2):126-32.
- Harden, C. L., Huff, J.S., Schwartz, T.H., Dubinsky, R.M., Zimmerman, R. D., Weinstein, S., Foltin, J. C., & Theodore, W.H. (2007). Reassessment: Neuroimaging in the emergency patient presenting with seizure (an evidence-based review) Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 69, no. 18: 1772-1780.
- Harden, C.L., Meador, K.J., Pennell, P.B., Hauser, W.A., Gronseth, G.S., French, J.A., & Wiebe S. et al. (2009b). Practice Parameter update: Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): Teratogenesis and perinatal outcomes Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology* 73, no. 2: 133-141.
- Harden CL, Pennell PB, Koppel BS, Hovinga CA, Gidal B, Meador KJ, Hopp J, Ting TY, Hauser WA, Thurman D, Kaplan PW, Robinson JN, French JA, Wiebe S, Wilner AN, Vazquez B, Holmes L, Krumholz A, Finnell R, Shafer PO, Le Guen C; American Academy of Neurology; American Epilepsy Society (2009c). Practice parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology* 14;73(2):142-9.
- Harden, C., Tomson, T., Gloss, D., Buchhalter, J., Cross, J.H., Donner, E., French, J.A., Gil-Nagel, A., Hesdorffer, D.C., Smithson, W.H., Spitz, M.C., Walczak, T.S., Sander, J.W., Ryvlin, P. (2017). Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*; 88(17):1674-1680.
- Health Canada (2016) Summary Basis of Decision (SBD) for BRIVLERA; Available from: <https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?lang=en&linkID=SBD00284>
- Health Quality Ontario (HQO) (2011). Making Evidence Relevant. Ontario Health Technology Assessment Service; Available from: <http://www.ontla.on.ca/library/repository/ser/255421/2011/2011no16dec.pdf>



References

- Health Quality Ontario (HQO) (2012). Epilepsy surgery: an evidence summary. Ontario Health Technology Assessment Service. July; 12(17):1-28. Available from: <http://www.hqontario.ca/en/documents/eds/2012/full-report-epil-surg.pdf>
- Herman, S.T. (2011). Early post stroke seizures: Is it time for prospective treatment trials? *Neurology*, 77, 1776-1778.
- Herman, S.T. (2009). Screening Bone Mineral Density in Epilepsy: A Call to Action, But What Action? *Epilepsy Currents*, 9(2), 44-46.
- Herrmann LK, Welter E, Berg AT, Perzynski AT, Van Doren JR, Sajatovic M. (2016). Epilepsy misconceptions and stigma reduction: Current status in Western countries. *Epilepsy & Behavior*; 60:165-173.
- Hirsh, E. & Genton, P. (2003). Antiepileptic drug-induced pharmacodynamic aggravation of seizures: does valproate have a lower potential? *CNS Drugs*, 17 (9):633-40.
- Hirtz, D., Ashwal, S., Berg, A., Bettis, D., Camfield, C., Camfield, P., Crumrine, P., Elterman, R., Schneider, S., & Shinnar, S. (2000). Practice parameter: Evaluating a first nonfebrile seizure in children. Report of the Quality Standards Subcommittee of the American Academy of Neurology, the Child Neurology Society, and the American Epilepsy Society. *Neurology* 55, no. 5: 616-623.
- Holmes, G. L. (1988). How to evaluate the patient after a first seizure. *Postgraduate medicine*, 83, no. 2: 199-209.
- Hopp, J.L. Nonepileptic Episodic Events (2019). *Continuum* (Minneapolis Minn) 25(2):492-507.
- Hoppe, C., & Elger, C.E. Depression in epilepsy: a critical review from a clinical perspective (2011). *Nature Reviews Neurology*. 12;7(8):462-72.
- Hunt, S., Russell, A., Smithson, W.H., Parsons, L., Robertson, I., Waddell, R., Irwin, B., Morrison, P.J., Morrow, J., & Craig, J. (2008). Topiramate in pregnancy Preliminary experience from the UK Epilepsy and Pregnancy Register. *Neurology* 71, no. 4: 272-276.
- Institute for Clinical and Evaluative Sciences and Ontario Brain Institute (2015). Brain Disorders in Ontario: Prevalence, Incidence and Costs from Health Administrative Data.
- Institute of Medicine. (2012). Epilepsy Across the Spectrum: Promoting Health and Understanding. Washington, DC: The National Academies Press.
- International League Against Epilepsy (2019) The black dog in your waiting room: Screening for depression in people with epilepsy. *Epilepsia* 21(4).
- Jackson, M. J., & Turkington, D. (2005). Depression and anxiety in epilepsy. *Journal of Neurology, Neurosurgery & Psychiatry* 76, no. suppl 1: i45-i47.
- Jacoby, A., Baker, G. A., Steen, N., Potts, P. & Chadwick, D. W. (1996). The Clinical Course of Epilepsy and Its Psychosocial Correlates: Findings from a U.K. Community Study. *Epilepsia*, 37, 148-161.
- Jain, P., Andrade, A., Donner, E., Dyment, D., Prasad, A.N., Goobie, S., Boycott, K., Lines, M., Snead, O.C. (2019) Development of criteria for epilepsy genetic testing in Ontario, Canada. *Canadian Journal of Neurological Sciences*; 46:7-13.
- Janousek, J., Barber, A., Goldman, L., & Klein, P. (2013). Obesity in adults with epilepsy. *Epilepsy & Behavior* 28, no. 3: 391-394.
- Jasper, H.H. (2012). Jasper's basic mechanisms of the epilepsies. Edited by Jeffrey Lloyd Noebels, Jeffrey Noebels, Massimo Avoli, Michael Rogawski, and Richard Olsen. Vol. 80. Oxford University Press.
- Jentink, J., Loane, M.A., Dolk, H., Barisic, I., Garne, E., Morris, J.K., & de Jong-van den Berg, L.T. (2010). EUROCAT Antiepileptic Study Working Group; Valproic acid monotherapy in pregnancy and major congenital malformations. *New England Journal of Medicine*, 362(23):2185-93.
- Johannessen, S.I., & Landmark, C.J. (2010) Antiepileptic drug interactions - principles and clinical implications. *Current Neuropharmacology* 8(3):254-267.
- Jones, J.E., Hermann, B.P., Barry, J.J., Gilliam, F., Kanner, A.M., & Meador, K.J. (2005). Clinical assessment of Axis I psychiatric morbidity in chronic epilepsy: a multicenter investigation. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 17(2):172-9.
- Kanner, A.M. (2013) The treatment of depressive disorders in epilepsy: what all neurologists should know. *Epilepsia*, 54 Suppl 1:3- 12. doi: 10.1111/epi.12100. Review.
- Kanner, A.M. (2016) Most antidepressant drugs are safe for patients with epilepsy at therapeutic doses: A review of the evidence. *Epilepsy & Behavior* 61: 282-286.
- Kerr, M.P., Mensah, S., Besag, F., de Toffol, B., Ettinger, A., Kanemoto, K., Kanner, A., Kemp, S., Krishnamoorthy, E., LaFrance, W.C. Jr., Mula, M., Schmitz, B., van Elst, L.T., Troller, J., & Wilson, S.J. (2011). International League of Epilepsy (ILAE) Commission on the Neuropsychiatric Aspects of Epilepsy. International consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy. *Epilepsia*, 52 (11):2133-8.
- King, M.A., Newton, M.R., Jackson, G.D., Fitt, G.J., Mitchell, L.A., Silvapulle, M.J., & Berkovic, S.F. (1998). Epileptology of the first- seizure presentation: a clinical, electroencephalographic, and magnetic resonance imaging study of 300 consecutive patients. *The Lancet*, 352, no. 9133: 1007-1011.



References

- Krumholz, A., Wiebe, S., Gronseth, G., Shinnar, S., Levisohn, P., Ting, T., & Hopp, J., et al. (2007). Practice Parameter: Evaluating an apparent unprovoked first seizure in adults (an evidence-based review) Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 69, no. 21.
- Kwan, P., Arzimanoglou, A., Berg, A.T., Brodie, M.G., Allen Hauser et al. (2010). Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task force of the ILAE Commission on Therapeutic strategies. *Epilepsia*, 51 (6): 1069.
- Lado, F., Spiegel, R., Masur, J.H., Boro, A., & Haut, S.R. (2008). Value of Routine Screening for Bone Demineralization in an Urban Population of Patients with Epilepsy. *Epilepsy Research*, 78 (2-3):155-160.
- LaFrance, W.C. Jr, Baker, G.A., Duncan, R., Goldstein, L.H., & Reuber, M. (2013) Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: a staged approach: a report from the International League Against Epilepsy Nonepileptic Seizures Task Force. *Epilepsia* 54 (11): 2005-18.
- MacCormick, J. M., McAlister, H., Crawford, J., French, J. K., Crozier, I., Shelling, A. N., & Skinner, J. R. (2009) Misdiagnosis of long QT syndrome as epilepsy at first presentation. *Annals of Emergency Medicine*, 54 (1), 26-32.
- Maguire MJ, Weston J, Singh J, Marson AG. (2014) Antidepressants for people with epilepsy and depression. *Cochrane Database of Systematic Reviews*, Issue 12. Art. No.: CD010682.
- Maschio, M. (2012). Brain Tumor-Related Epilepsy. *Current Neuropharmacology*, 10(2): 124-133.
- Margulis, A. V., Mitchell, A.A., Gilboa, S.M., Werler, M.M., Mittleman, M.A., Glynn, R.J., & Hernandez-Diaz, S. (2012) Use of topiramate in pregnancy and risk of oral clefts. *American Journal of Obstetrics and Gynecology* 207, no. 5: 405-e1.
- Mercimek-Mahmutoglu, S., Patel, J., Cordeiro, D., Hewson, S., Callen, D., Donner, E. J., & Snead, O. C. (2015). Diagnostic yield of genetic testing in epileptic encephalopathy in childhood. *Epilepsia*, 56(5), 707-716.
- Mula, M., Kanner, A.M., Schmitz, B., & Schachter, S. (2013) Antiepileptic drugs and suicidality: an expert consensus statement from the Task Force on Therapeutic Strategies of the ILAE Commission on Neuropsychobiology. *Epilepsia*; 54(1):199-203.
- Myers, K. A., Johnstone, D. L., & Dymont, D. A. (2019). Epilepsy genetics: Current knowledge, applications, and future directions. *Clinical Genetics*, 95(1), 95-111.
- Nanau, R.M., & Neuman, M.G. (2013). Adverse drug reactions induced by valproic acid. *Clinical Biochemistry* 46, no. 15: 1323-1338.
- National Institute for Health and Clinical Excellence (NICE). (2012). The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (update). (Clinical Guideline 137). Found at: <http://guidance.nice.org.uk/CG137>.
- Pack, A.M., Olarte, L.S., Morrell, M.J., Flaster, E., Resor, S.R., & Shane, E. (2003). Bone mineral density in an outpatient population receiving enzyme-inducing antiepileptic drugs. *Epilepsy Behaviour*, 4:169-174.
- Panayiotopoulos, C. P. (1998). Significance of the EEG after the first afebrile seizure. *Archives of Disease in Childhood*, 78, no. 6: 575-577.
- Patel, T. (2018) Managing Seizure Disorders in Adults. Pharmacy Practice & Business National Continuing Education Program
- Patsalos, P.N., Berry, D.J., Bourgeois, B., Cloyd, J.C., Glauser, T.A., Johannessen, S.I., Leppik, I.E., Tomson, T., & Perucca, E. (2008). Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia*, 49, no. 7 1239-1276.
- Perry, M.S. (2020). Age is just a number: adults deserve the same access to genetic testing as children. *Epilepsy Currents*; 20(1):14-15.
- Perucca, E., Dulac, O., Shorvon, S. et al. (2001). Harnessing the Clinical Potential of Antiepileptic Drug Therapy. *CNS Drugs* 15, 609-621.
- Perucca, E., Gram, L., Avanzini, G., & Dulac, O. (1998). Antiepileptic drugs as a cause of worsening seizures. *Epilepsia*, 39, (1):5-17.
- Perucca, E & Tomson, T. (2011) The pharmacological treatment of epilepsy in adults. *Lancet Neurology*; 10(5):446-56.
- Petty, S.J., O'Brien, T.J., Wark, J.D. (2007) Anti-epileptic medication and bone health. *Osteoporosis International*, 18,129-142.
- RamachandranNair, R. & Jack, S.M. (2016) SUDEP: What do adult patients want to know? *Epilepsy & Behavior* 64 (Pt A):195-199.
- Ramachandrannair, R., Jack, S.M., Meaney, B.F., & Ronen, G.M. (2013) SUDEP: what do parents want to know? *Epilepsy & Behavior*; 29(3):560-4.



References

- Rogawski, M.A. (2012). Migraine and Epilepsy—Shared Mechanisms within the Family of Episodic Disorders. In: Noebels JL, Avoli M, Rogawski MA, et al. editors. *Jasper's Basic Mechanisms of the Epilepsies* [Internet]. 4th edition. Bethesda (MD): National Center for Biotechnology Information (US); Available from: <http://www.ncbi.nlm.nih.gov/books/NBK98193/>
- Scheffer, I.E., Berkovic, S, Capovilla, G, Connolly M.B., French, J, Guilhoto, L, Hirsch, E, Jain, S, Mathern, G.W., Moshé S.L., Nordli, D.R., Perucca, E, Tomson, T., Wiebe, S, Zhang Y.H., Zuberi S.M. (2017) ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*; 58(4):512-521.
- Shapiro, M.J., & Cole A.J. (2011) Alcohol and toxin induced seizures, Chapter 92. In Shorvon, S., Andermann, F., & Guerrini, R. (Eds.) *The Causes of Epilepsy*. Cambridge: Cambridge University Press, 2011.
- Shifren, J.L., & Gass, M.L. (2014) NAMS Recommendations for Clinical Care of Midlife Women Working Group. The North American Menopause Society recommendations for clinical care of midlife women. *Menopause*; 21(10):1038-62.
- Stephen, L.J., Harden, C., Tomson, T., & Brodie, M.J. Management of epilepsy in women. (2019) *Lancet Neurology*; 18(5):481-491.
- Stokes, T., Shaw, E.J., Juarez-Garcia, A., Camosso-Stefinovic, J. & Baker, R. (2004). Clinical guidelines and evidence review for the epilepsies: diagnosis and management in adults and children in primary and secondary care. London: Royal College of General Practitioners.
- Tellez-Zenteno, J.F., Pondal-Sordo, M., Matijevic, S., & Wiebe, S. (2004). National and regional prevalence of self-reported epilepsy in Canada. *Epilepsia* 45 (12), 1623-1629.
- Tellez-Zenteno, J.F., Patten, S.B., Jette, N., Williams, J., & Wiebe, S. (2007) Psychiatric comorbidity in epilepsy: a population based analysis. *Epilepsia*, 48:2336-44.
- Trivedi, M.H., & Kurian, B.T. (2007). Managing depressive disorders in patients with epilepsy. *Psychiatry* (Edgmont), 4, no. 1: 26.
- Vining, E. & Freeman, J.M. (1986). Management of nonfebrile seizures. *Pediatrics in Review* 8, no. 6 (1986): 185-190.
- Wallace, H., Shorvon, S., & Tallis, R. (1998). Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2 052 922 and age-specific fertility rates of women with epilepsy. *The Lancet*, 352, no. 9145 (1998): 1970-1973.
- West, S., Nevitt, S.J., Cotton, J., Gandhi, S., Weston, J., Sudan, A., Ramirez, R., & Newton, R. (2019) Surgery for epilepsy. *Cochrane Database of Systematic Reviews* Issue 6. Art. No.: CD010541. DOI: 10.1002/14651858.CD010541.pub3
- Weston, J., Bromley, R., Jackson, C.F., Adab, N., Clayton-Smith, J., Greenhalgh, J., Hounscome, J., McKay, A.J., Tudur Smith, C., Marson, A.G. (2016). Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. *Cochrane Database of Systematic Reviews*. 7;11:CD010224.
- Wiebe, S., Bellhouse, D.R., Fallahay, & C., Eliasziw, M. (1999). Burden of epilepsy: the Ontario Health Survey. *Canadian Journal of Neurological Sciences*; 26 (4), 263-270.
- Winterfeld, U., Merlob, P., Baud, D., Rousson, V., Panchaud, A., Rothuizen, L.E., Bernard, N., Vial, T., Yates, L.M., Pistelli, A., Ellfolk, M., Eleftheriou, G., de Vries, L.C., Jonville-Bera, A.P., Kadioglu, M., Biollaz, J., & Buclin, T. (2016). Pregnancy outcome following maternal exposure to pregabalin may call for concern. *Neurology* 14;86(24):2251-7.
- Zaccara, G., Perucca, E.. (2014) Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. *Epileptic Disorders* 16(4):409-31.
- Zaidi, A., Clough, P., Cooper, P., Scheepers, B., & Fitzpatrick, A. P. (2000). Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause. *Journal of the American College of Cardiology*, 36(1), 181-184.



Appendix 1: Original 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. Jorge Burneo	Adult Academic Neurologist	London Health Sciences Centre
Dr. Sandrine De Ribaupierre	Paediatric Neurosurgeon	London Health Sciences Centre
Pat Elliot-Miller	CNE and VP Patient Services	Children's Hospital of Eastern Ontario
Elizabeth Ferguson	Director, Centre for Brain and Behavior	The Hospital for Sick Children
Laurie Gould	EVP Patient-Centred Care	London Health Sciences Centre
Dr. Ayman Hassan	Community Adult Neurologist	Thunder Bay Regional Health Sciences Centre
Kathryn LeBlanc	Director, Neurosciences	Hamilton Health Sciences
Dr. Athen MacDonald	Academic Paediatric Neurologist	Kingston General Hospital
David McNeil	Vice President Clinical Programs/CNO	Health Sciences North
Janet Newton	Clinical Director	University Health Network
Kirk Nysten	Director, Outreach	Ontario Brain Institute
Dr. Rajesh RamachandranNair	Academic Paediatric Neurologist	McMaster Children's Hospital / Hamilton Health Sciences
Mary Secco	Director of Strategic Initiatives	Epilepsy Southwestern Ontario
Dr. Laurene Sellers	Family Practice Physician	Kitchener, Ontario
Dr. Michelle Shapiro	Adult Academic Neurologist	Hamilton Health Sciences
Rosie Smith	Director of Adult Services	Epilepsy Toronto
Mike Tierney	VP Clinical Programs	The Ottawa Hospital
Dr. Taufik Valiante	Adult Neurosurgeon	University Health Network
Dr. Sharon Whiting	Paediatric Neurologist	Children's Hospital of Eastern Ontario



Appendix 2: Examples of Electroclinical Syndrome Arranged by Age at Onset

Age at Onset	Electroclinical Syndromes (Berg et al., 2010)
Neonatal period	<ul style="list-style-type: none"> • Benign familial neonatal epilepsy (BFNE) • Early myoclonic encephalopathy (EME) • Ohtahara syndrome
Infancy	<ul style="list-style-type: none"> • Epilepsy of infancy with migrating focal seizures • West syndrome • Myoclonic epilepsy in infancy (MEI) • Benign infantile epilepsy • Benign familial infantile epilepsy • Dravet syndrome • Myoclonic encephalopathy in nonprogressive disorders
Childhood	<ul style="list-style-type: none"> • Febrile seizures plus (FS+) (can start in infancy) • Panayiotopoulos syndrome • Epilepsy with myoclonic atonic (previously astatic) seizures • Benign epilepsy with centrotemporal spikes (BECTS) • Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE) • Late onset childhood occipital epilepsy (Gastaut type) • Epilepsy with myoclonic absences • Lennox-Gastaut syndrome • Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS) • Landau-Kleffner syndrome (LKS) • Childhood absence epilepsy (CAE)
Adolescence – Adult	<ul style="list-style-type: none"> • Juvenile absence epilepsy (JAE) • Juvenile myoclonic epilepsy (JME) • Epilepsy with generalized tonic-clonic seizures alone • Progressive myoclonus epilepsies (PME) • Autosomal dominant epilepsy with auditory features (ADEAF) • Other familial temporal lobe epilepsies
Less specific age relationship	<ul style="list-style-type: none"> • Familial focal epilepsy with variable foci (childhood to adult) • Reflex epilepsies



Appendix 3: ASD Dosing and Titration (updated 2020)

3.1: Dosing recommendations for children (Perucca et al., 2001; Donner & Snead, 2006; Health Canada, 2016; Abou-Khalil, 2019)

Drug	Initial Dose	Administration and Titration	Usual Maintenance Dose
Brivaracetam	1 mg/kg/day to 2.5 mg/kg/day (weighing 11kg to <20 kg) 1mg/kg/day to 2mg/kg/day (weighing 20kg to <50kg) 50mg/day to 100mg/day (weighing 50kg or more)	<ul style="list-style-type: none"> ▪ Given 2x/day ▪ Based on clinical response and tolerability, adjust dose within maintenance dose range 	1 mg/kg/day to 5mg/kg/day (weighing 11kg to <20kg) 1mg/kg/day to 4mg/kg/day (weighing 20kg to <50kg) 50-200 mg/day (weighing 50 kg or more)
Carbamazepine	5-10 mg/kg/day	<ul style="list-style-type: none"> ▪ Given 2-3x/day ▪ 5-10mg/kg every 5-7 days 	20 – 30 mg/kg/day
Clobazam	0.1 mg/kg/day	<ul style="list-style-type: none"> ▪ Given 1-2x/day ▪ 0.1 mg/kg/day every 5- 7 days 	1.0 mg/kg/day
Clonazepam	0.01 - 0.03 mg/kg/day	<ul style="list-style-type: none"> ▪ Given 2-3x/day ▪ 0.25 to 0.50 mg every 3 days 	0.1 – 0.2 mg/kg/day
Eslicarbazepine	10 mg/kg/day	<ul style="list-style-type: none"> ▪ Given 1x/day ▪ 5 mg/kg every 7 days 	20 – 60 mg/kg/day
Ethosuximide	10 – 15 mg/kg/day	<ul style="list-style-type: none"> ▪ Given 1-2x/day ▪ 5 mg/kg/day every 7 days 	20 – 30 mg/kg/day
Felbamate	15 mg/kg/day	<ul style="list-style-type: none"> ▪ Given 3-4x/day ▪ 5 mg/kg/day every 7 days 	15 – 45 mg/kg/day
Lamotrigine (monotherapy)	0.3 mg/kg/day	<ul style="list-style-type: none"> ▪ Given 1-2x/day ▪ 0.3 mg/kg/day every 7-14 days 	5 - 15 mg/kg/day
Lamotrigine (with valproic acid)	0.15 mg/kg/day	<ul style="list-style-type: none"> ▪ Given 1-2x/day ▪ 0.15 – 0.3 mg/kg/day every 7-14 days 	1 - 5 mg/kg/day
Lamotrigine (with enzyme inducers)	0.6 mg/kg/day	<ul style="list-style-type: none"> ▪ Given 1-2x/day ▪ 1.2 mg/kg/day every 7-14 days 	5 – 15 mg/kg/day
Levetiracetam	10 mg/kg/day to 20 mg/kg/day	<ul style="list-style-type: none"> ▪ Given 2-3x/day ▪ 20 mg/kg/day every 7 days 	20 – 60 mg/kg/day 60 mg/kg/day up to 100
Oxcarbazepine	8- 10 mg/kg/day	<ul style="list-style-type: none"> ▪ Given 2x/day ▪ 5-7 mg/kg/day every 3-7 days 	20 mg/kg/day to 50 mg/kg/day
Perampanel (7-17 years of age)	2 mg/day	<ul style="list-style-type: none"> ▪ Given 1x/day ▪ 2 mg/day every 7 days 	8 – 12 mg/day
Phenobarbital	1 – 3 mg/kg/day	<ul style="list-style-type: none"> ▪ Given 1x/day ▪ 1 mg/kg/day every 7-14 days 	3 – 8 mg/kg/day
Phenytoin	5 – 7 mg/kg/day	<ul style="list-style-type: none"> ▪ Given 2-3x/day ▪ Titration not necessary 	5 – 15 mg/kg/day
Primidone	10 mg/kg/day	<ul style="list-style-type: none"> ▪ Given 2-4x/day ▪ Titration not necessary 	5 – 25 mg/kg/day
Rufinamide	10 mg/kg/day 5 mg/kg/day (with valproate)	<ul style="list-style-type: none"> ▪ Given 2x/day ▪ 10 mg/kg/day every other day ▪ 5 mg/kg/day every other day (with valproate) 	20 – 45 mg/kg/day 20 – 30 mg/kg/day (with valproate)
Topiramate	1 – 3 mg/kg/day	<ul style="list-style-type: none"> ▪ Given 1-2x/day ▪ 1-3 mg/kg/day every 7-14 days 	6 mg/kg/day to 8 mg/kg/day (up to 30 has been reported)
Valproic acid	10 mg/kg/day	<ul style="list-style-type: none"> ▪ Given 2-3x/day ▪ 5 – 10 mg/kg/day every 7 days 	30 – 60 mg/kg/day
Vigabatrin	20 mg/kg/day 50 mg/kg/day (infantile spasms)	<ul style="list-style-type: none"> ▪ Given 2x/day ▪ 20 mg/kg/day every 7 days ▪ Increase to 100 mg/kg/day after 5 days (infantile spasms) 	40 – 60 mg/kg/day 100 - 150 mg/kg/day (infantile spasms)
Zonisamide	1 mg/kg/day	<ul style="list-style-type: none"> ▪ Given 1-2x/day ▪ 2 mg/kg/day every 14 days 	4 – 12 mg/kg/day



3.2: Dosing recommendations for adults (Perucca, 2011; Health Canada, 2016; Patel, 2018; Abou-Khalil, 2019)

Drug	Initial Dose	Administration and Titration	Usual Maintenance Dose
Brivaracetam	100 mg/day	<ul style="list-style-type: none"> Given 2x/day Based on clinical response and tolerability, adjust dose within maintenance dose range. 	50 – 200 mg/day
Carbamazepine	100 – 200 mg/day	<ul style="list-style-type: none"> Given 2-4x/day 200 mg/day every 5-7 days 	200 – 2000 mg/day
Clobazam	5-10 mg/day	<ul style="list-style-type: none"> Given 1-2x/day 10 mg/day every 7 days 	10 – 40 mg/day
Clonazepam	1.5 mg/day	<ul style="list-style-type: none"> Given 3x/day 0.5 – 1 mg/day every 3 days 	2 – 20 mg/day
Eslicarbazepine	400 mg/day	<ul style="list-style-type: none"> Given 1x/day 400/mg/day every 7 days 	800 – 1200 mg/day
Ethosuximide	250 – 500 mg/day 1-2x daily	<ul style="list-style-type: none"> Given 3x/day 250 mg/day every 5-7 days 	500 – 1500 mg/day
Gabapentin	300 – 900 mg/day	<ul style="list-style-type: none"> Given 2- 4x/day 300 mg/day every 5-7 days 	900 – 4800 mg/day
Lacosamide	100 mg/day	<ul style="list-style-type: none"> Given 1-2x/day 100 mg/day every 1-2 weeks 	200 – 600 mg/day
Lamotrigine (monotherapy)	25 mg/day	<ul style="list-style-type: none"> Given 1-2x/day 25 mg/day for 2 weeks, followed by 50 mg/day for 2 weeks, then 100 mg/day. Increase as needed by 100 mg every 2 weeks. 	100 – 400 mg/day
Lamotrigine (with valproic acid)	25 mg/day every other day	<ul style="list-style-type: none"> Given 1-2x/day Slower rate of titration when combined with valproic acid. 	100 – 400 mg/day
Lamotrigine (with enzyme inducers)	25 – 50 mg/day	<ul style="list-style-type: none"> 25 – 50 mg/day for 2 weeks Increase to 50 or 100 mg/day for 2 weeks. Increase as needed by 50-100 mg/day every 1-2 weeks. 	
Levetiracetam	500 – 1000 mg/day	<ul style="list-style-type: none"> Given 1-2x/day 250-500 mg/day every 5-7 days 	1000 – 4000 mg/day
Oxcarbazepine	300 – 600 mg/day	<ul style="list-style-type: none"> Given 1-2x/day 300 mg/day every 7 days 	600 – 2400 mg/day
Perampanel	2 mg/day (in absence of enzyme-inducing ASDs) 4 mg/day (with enzyme-inducing ASD)	<ul style="list-style-type: none"> Given 1x/day at bedtime Increments of 2 mg/day every 14-30 days 	4 – 12 mg/day
Phenobarbital	30 – 60 mg/day at bedtime	<ul style="list-style-type: none"> Given 1-2x/day 30-60 mg/day every 2 weeks 	60 – 240 mg/day
Phenytoin	100 mg/day	<ul style="list-style-type: none"> Given 1-4x/day Titration not necessary 	200 – 600 mg/day
Pregabalin	75 – 150 mg/day	<ul style="list-style-type: none"> Given 2-3x/day 75-150 mg/day every 7 days 	150 – 600 mg/day
Primidone	50 – 125 mg/day	<ul style="list-style-type: none"> Given 2-3x/day 50-125 mg/day every 3-7 days 	750 – 1500 mg/day
Rufinamide	400 mg/day	<ul style="list-style-type: none"> Given 2x/day 400 mg/day every other day 	400 – 3200 mg/day
Topiramate	25 mg/day	<ul style="list-style-type: none"> Given 2x/day 25-50 mg/day every 7 days 	100 – 400 mg/day
Valproic acid	500 mg/day	<ul style="list-style-type: none"> Given 2-4x/day 250 mg/day every 7 days 	500 – 4000 mg/day
Vigabatrin	500 mg/day	<ul style="list-style-type: none"> Given 2x/day 500 mg/day every 7 days 	1000 – 3000 mg/day



Appendix 4: Outline for Seizure Assessment

Features of a seizure (Hirtz et al, 2000; Krumholz et al, 2007)	
Associated factors	<ul style="list-style-type: none"> • Age • Family history • Developmental status • Behavior • Health at seizure onset • Precipitating events other than illness—trauma, toxins
First Nonfebrile Seizure	<ul style="list-style-type: none"> • Health at seizure onset—febrile, ill, exposed to illness, complaints of not feeling well, sleep deprived • Symptoms during seizure (ictal) • Aura: Subjective sensations • Behavior: Mood or behavioral changes before the seizure • Preictal symptoms: Described by patient or witnessed • Vocal: Cry or gasp, slurring of words, garbled speech • Motor: Head or eye turning, eye deviation, posturing, jerking (rhythmic), stiffening, automatisms (purposeless repetitive movements such as picking at clothing, lip smacking); generalized or focal movements • Respiration: Change in breathing pattern, cessation of breathing, cyanosis • Autonomic: Pupillary dilatation, drooling, change in respiratory or heart rate, incontinence, pallor, vomiting • Loss of consciousness or inability to understand or speak • Duration of seizure
Symptoms following seizure (postictal)	<ul style="list-style-type: none"> • Amnesia for events • Confusion • Lethargy • Sleepiness • Headaches and muscle aches • Transient focal weakness (Todd’s paresis) • Nausea or vomiting



Appendix 5: Community Epilepsy Agencies in Ontario

<p>Epilepsy Durham Region 310 Byron Street South, Unit 3, Whitby, Ontario L1N 4P8 Tel: 905-430-3090 Fax: 905-430-3080 Email: support@epilepsydurham.com Web: www.epilepsydurham.com</p>	<p>Epilepsy Niagara 4635B Queen Street, Niagara Falls, Ontario, L2E 2L7 Tel: 289-296-3460 Fax: 866-293-6300 Email: info@epilepsyniagara.org Web: www.epilepsyniagara.org</p>
<p>Epilepsy North Bay North Bay, Ontario Tel: 705-494-8199 Email: communications@epilepsysupport.ca</p>	<p>Epilepsy Ontario Unit 15 – 470 North Rivermede Road, Concord, Ontario, L4K 3R8 Tel: 905-738-9431 or 1-800-463-1119 (toll-free) Email: info@epilepsyontario.org Web: www.epilepsyontario.org</p>
<p>Epilepsy Ottawa 211 Bronson Ave, Suite 207, Ottawa, Ontario, K1R 6H5 Tel: 613-594-9255 Email: info@epilepsyottawa.ca Web: www.epilepsyottawa.ca</p>	<p>Epilepsy Peterborough & Area Unit 6, Charlotte Mews, 203 Simcoe Street, Peterborough, Ontario Mailing: P.O. Box 2453, Peterborough, ON K9J 7Y8 Tel: 705-876-0311 or 1-800-463-1119 (toll-free) Fax: 705-876-0109 Email: epilepsytbo@yahoo.ca</p>
<p>Epilepsy Sault Ste Marie Sault Ste. Marie, Ontario Tel: 705-254-8565 Email: jammasp@shaw.ca</p>	<p>Epilepsy Simcoe County 72 Ross Street, Unit 10, Barrie, Ontario, L4N 1G3 Tel: 705-737-3132 Fax: 705-737-5045 Email: epilepsysimcoecounty@rogers.com</p>
<p>Epilepsy South Central Ontario — Halton Peel Hamilton 2155 Dunwin Drive, Unit 5, Mississauga, Ontario, L5L 4M1 Tel: 905-450-1900 or 1-855-734-2111 (toll-free) Email: info@epilepsysco.org Web: www.epilepsysco.org</p>	<p>Epilepsy South Central Ontario — K-W Guelph 351-B Louisa Street, Kitchener, Ontario, N2H 5N1 Tel: 905-450-1900 Fax: 905-820-9393 Email: info@epilepsysco.org Web: www.epilepsysco.org</p>
<p>Epilepsy South Eastern Ontario 920 Princess Street, Unit 370, Kingston, Ontario, K7L 1H1 Tel: 613-542-6222 Fax: 613-548-4162 Email: admin@epilepsyresource.org Web: www.epilepsyresource.org</p>	<p>Epilepsy Southwestern Ontario— Chatham/Kent Sarnia/Lambton Windsor/Essex 797 York Street, Unit 3, London, Ontario, N5W 6A8 Tel: 519-433-4073 Tel (Chatham/Kent, Sarnia/Lambton): 519-365-5131 Tel (Windsor/Essex): 519-890-6614 Fax: 519-433-4079 Email: info@epilepsyswo.ca Website: www.epilepsyswo.ca</p>
<p>Epilepsy Sudbury Sudbury, Ontario Tel: 705-885-2127 Email: Sudbury@epilepsyontario.org</p>	<p>Epilepsy Toronto 468 Queen St. East, Suite 210, Toronto, Ontario, M5A 1T7 Tel: 416-964-9095 Fax: 416-964-2492 Email: info@epilepsytoronto.org Web: www.epilepsytoronto.org</p>

**Epilepsy York Region**

6356 Main Street, Stouffville, Ontario, L4A 1G9

Tel: 905-640-8000

Fax: 905-640-0038

Email: info@epilepsyork.org

Web: www.epilepsyork.org

Timmins Seizure & Brain Injury Centre

733 Ross Ave. East, Timmins, Ontario, P4N 8S8

Tel: 705-264-2933

Fax: 705-264-0350

Email: sabicr1@eastlink.ca

Web: www.seizurebraininjurycentre.com



Appendix 6: Description of Some of the Comorbidities Associated with Epilepsy

ADHD: Attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with prevalence in the general population of 5-7%. The prevalence is increased to 20-30% in children with epilepsy. If co-morbid ADHD occurs independent of seizure effect, specific ADHD treatment should be initiated (Brown, Becker, Pollard, & Anderson, 2013).

Alcohol: Seizures may occur due to alcohol withdrawal. These are most often generalized tonic-clonic seizures occurring within 6-48 hours after cessation of alcohol use. These seizures are provoked and are therefore not considered to be part of a definition of epilepsy. These types of seizures should not be treated with long-term administration of anti-epileptic drugs. The EEGs in these patients are usually normal. It is important to note, however, that alcoholic patients may have confounding causes for seizures and epilepsy including head trauma, subdural hematoma, stroke, abscess, meningitis and metabolic derangements. In cases of structural causes for epilepsy in these patients, long-term administration of anti-epileptic drugs would be appropriate. Poor compliance, drug overuse, and drug-alcohol interactions may be issues. In all patients with alcoholism, the treatment of alcohol dependence is extremely important (Shapiro & Cole, 2011; Gilhus, Barnes, & Brainin, 2011).

Autism Spectrum Disorder: Epilepsy and autism are co-morbid phenomena and may be related to a common brain abnormality. Epilepsy occurs in 10-30% of individuals with autism, with a higher incidence in girls. EEG is not recommended routinely in children with autism (American Academy of Neurology and the Child Neurology Society, 2000).

Intellectual Developmental Disorder/Intellectual Disability (ID): Estimates of the prevalence of epilepsy among patients with an intellectual disability range from 14% to 44%, a significant excess compared with the general population (Bowley & Kerr, 2000). The risk of

potential behavioural side effects should be considered when prescribing ASDs to patients with ID and epilepsy. Healthcare professionals and/or community epilepsy agencies should play an active role to help the patient and caregiver obtain appropriate support and services within the educational system, workplace and community.

Migraine: The prevalence of migraine in populations of individuals with epilepsy is estimated at 8-24%, approximately twice that in the normal population (Rogawski, 2012). Children with migraine may have an increased incidence of epilepsy. In many cases it may be beneficial to treat the two conditions with the same medications. There is extensive evidence from randomized controlled clinical trials that divalproex sodium (valproate) and topiramate are effective in preventing migraine attacks (Rogawski, 2012).

Neoplasia: Seizures and epilepsy are common in people with brain tumours. They are particularly common with slow-growing gliomas, meningiomas located in the convexity of the brain, and with metastatic brain tumours. These patients present a complex therapeutic profile and the choice of anti-seizure drugs is challenging because brain tumour-related epilepsy (BTRE) is often drug-resistant and has a strong impact on quality of life. In brain tumour patients, the presence of epilepsy is considered the most important risk factor for long-term disability. In BTRE, ASDs with fewer drug interactions and fewer side effects are preferred (Maschio, 2012).

Obesity: Obesity is a common co-morbidity for adults and children with epilepsy (Janousek, Barber, Goldman, & Klein, 2013; Daniels, Nick, Lui, Cassedy, Glauser, 2009). Since obesity has a number of concomitant health risks, it is suggested that all patients with epilepsy and obesity be appropriately referred for treatment/weight loss. This can be done through the patient's primary care physician.



With regards to epilepsy, the choice of medication for a given patient may well be influenced by this co-morbidity as a number of anti-seizure medications including valproic acid, carbamazepine, gabapentin, and vigabatrin are known to be associated with weight gain. In addition, some medications including topiramate are associated with weight loss (Biton, 2006).

Osteoporosis/Fractures: Treatment with various anti-seizure drugs including phenytoin, carbamazepine, phenobarbital, and valproic acid have been implicated in decreased bone mineral density. While rates from 20-75% have been reported in cross-sectional studies (Pack, 2003; Petty, O'Brien, & Wark, 2007), precise prevalence rates are not known (Lado, Spiegel, Masur, Boro, & Haut, 2008). There is also an increased risk of fracture among patients with epilepsy, with twice the increased risk of pathological fracture compared to the general population. This is likely at least in part due to higher rates of decreased bone mineral density in these patients. Screening for osteopenia and osteoporosis is recommended for patients receiving treatment with anti-seizure drugs (Herman, 2009). The standard screening tool is

the dual energy x-ray absorptiometry (DEXA) scan.

Stroke: Stroke is the most common cause of epilepsy in patients 65 years old and over, the group with the highest incidence of epilepsy overall (Wallace, Shorvon, & Tallis, 1998; Bergey, 2004). It can, however, be a cause of epilepsy in patients of all ages. In older patients, stroke should always be sought as a potential cause of new-onset seizures/epilepsy. In patients of all ages with presumed structural causes of seizures/epilepsy, stroke should be sought as a potential cause. Epilepsy caused by stroke is more common in hemorrhagic stroke and venous sinus thrombosis. However, there is no strong evidence for the role for seizure prophylaxis with medication in these cases, when acute head trauma is not also incurred (Herman, 2011). When choosing a medication, tolerability, cost, and potential interactions with other drugs should be considered (Bergey, 2004; Bleck, 2012; Herman, 2011).

