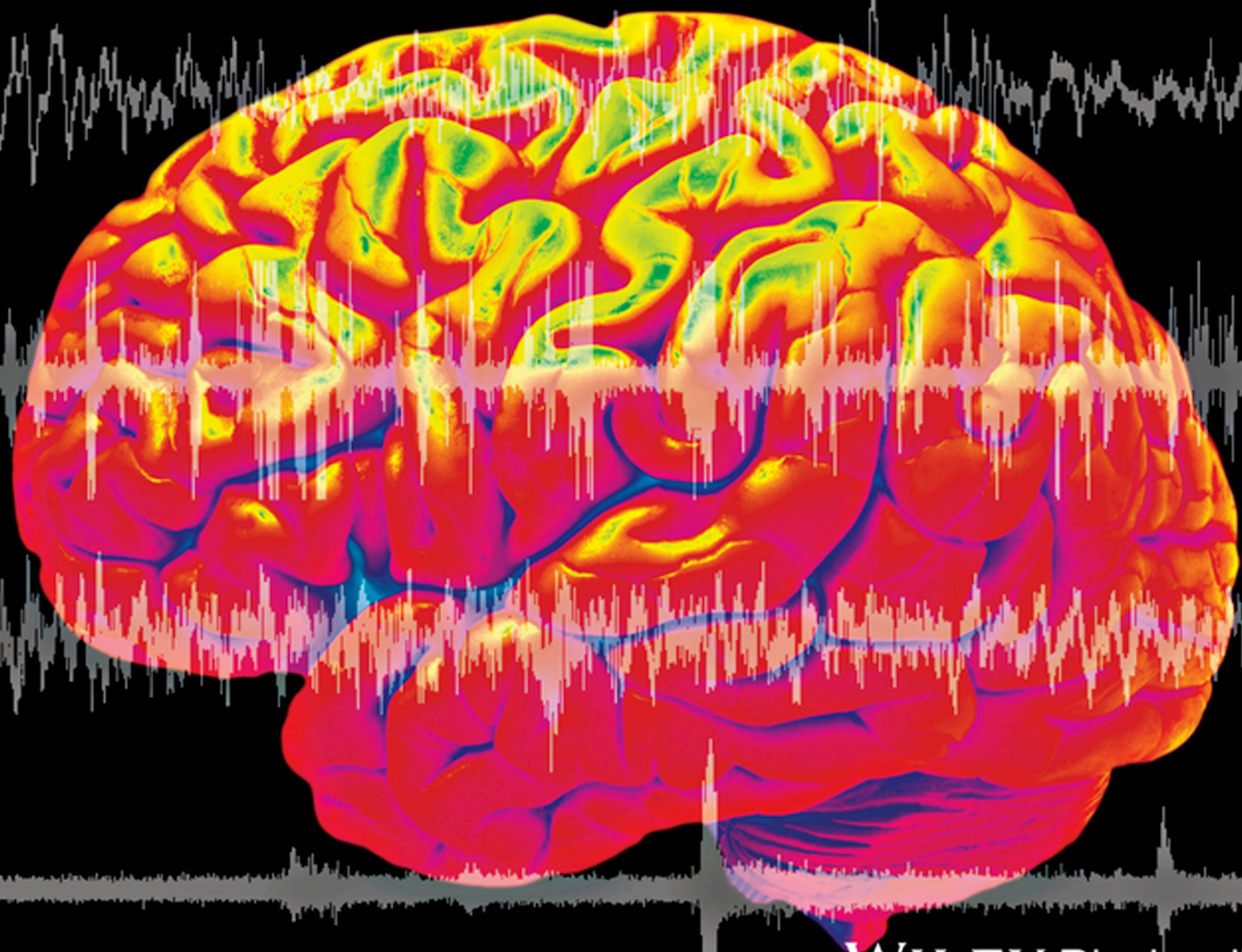


# Epilepsy

and the Interictal State

CO-MORBIDITIES AND QUALITY OF LIFE

Erik K. St. Louis • David M. Ficker • Terence J. O'Brien



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# **Epilepsy and the interictal state**

Co-morbidities and quality of life



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Co-morbidities and quality of life

EDITED BY

## **Erik K. St. Louis**

Department of Neurology  
Mayo Clinic and Foundation  
USA

## **David M. Ficker**

University of Cincinnati Neuroscience Institute Epilepsy Center  
Department of Neurology  
University of Cincinnati Academic Health Center  
USA

## **Terence J. O'Brien**

Professor of Medicine  
Royal Melbourne Hospital  
Australia

**WILEY**

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The Editors wish to dedicate this book foremost to our families (Kerith, Aren, Kjersti, Siri, Ken and Karen St. Louis; Angela, Lauren, Anna and Kerstin Ficker; and Louise, William, Patrick, Lawrence and Alice O'Brien); to our epilepsy care mentors (Gregory D. Cascino, Frank W. Sharbrough, and Elson L. So); to all the chapter authors; and especially, to our patients.





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# List of contributors

**Sophia J. Adams**

Melbourne Neuropsychiatry Centre  
University of Melbourne  
and  
Neuropsychiatry Unit  
Royal Melbourne Hospital  
Australia

**Gus Baker**

Walton Centre for Neurology & Neurosurgery  
University of Liverpool  
UK

**Yvan A. Bamps**

Department of Behavioral Sciences and  
Health Education  
Rollins School of Public Health  
Emory University  
USA

**Selim R. Benbadis**

Department of Neurology & Neurosurgery  
University of South Florida  
and  
Tampa General Hospital  
USA

**Frank M.C. Besag**

South Essex Partnership University  
NHS Foundation Trust  
Twinwoods Health Resource Centre  
Bedford and Institute of Psychiatry  
UK

**Colleen K. Dilorio**

Department of Behavioral Sciences and  
Health Education  
Rollins School of Public Health  
Emory University  
USA

**Joe Drazkowski**

Department of Neurology  
Mayo Clinic  
USA

**David W. Dunn**

Department of Psychiatry and Neurology  
Indiana University School of Medicine  
USA

**Jonathan C. Edwards**

Department of Neurosciences  
Medical University of South Carolina  
USA

**Dana Ekstein**

Epilepsy Center  
Department of Neurology  
Hadassah University Medical Center  
Israel

**John O. Elliott**

Department of Medical Education  
Ohio Health Riverside Methodist Hospital  
and  
College of Social Work  
Ohio State University  
USA

**Ashley M. Enke**

Creighton University  
USA

**David M. Ficker**

University of Cincinnati Neuroscience Institute  
Epilepsy Center  
Department of Neurology  
University of Cincinnati Academic Health Center  
USA

**Frank G. Gilliam**

Department of Neurology, Penn State University  
Hershey, USA

**Keith D. Hill**

School of Physiotherapy and Exercise Science  
Curtin University  
and  
Department of Allied Health  
La Trobe University  
Northern Health and National Ageing  
Research Institute  
Australia

**R. Edward Hogan**

Washington University in St. Louis  
Adult Epilepsy Section, Department of Neurology  
USA

**Ann Jacoby**

Department of Public Health and Policy  
Institute of Psychology, Health and Society  
University of Liverpool  
UK

**Robert D. Jones**

Department of Neurology  
University of Iowa  
USA

**Simon Jones**

Melbourne Neuropsychiatry Centre  
University of Melbourne  
and  
Neuropsychiatry Unit  
Royal Melbourne Hospital  
Australia

**Irakli Kaolani**

Department of Neurology  
Mayo Clinic  
USA

**Rosemarie Kobau**

Division of Population Health  
Centers for Disease Control and Prevention  
USA

**Vladimír Komárek**

Department of Pediatric Neurology  
2nd Faculty of Medicine  
Charles University  
Motol University Hospital  
Czech Republic

**William G. Kronenberger**

Department of Psychiatry  
Indiana University School of Medicine  
USA

**Ekrem Kutluay**

Department of Neurosciences  
Medical University of South Carolina  
USA

**Beth A. Leeman**

Department of Neurology  
Emory University  
USA

**Esmeralda L. Park**

Rush Epilepsy Center  
Rush University Medical Center  
USA

**Luigi Maccotta**

Washington University in St. Louis  
Adult Epilepsy Section, Department of Neurology  
USA

**Bláthnaid McCoy**

Division of Neurology  
The Hospital for Sick Children  
Canada

**Kimford J. Meador**

Department of Neurology  
Emory University  
USA

**J. Layne Moore**

Department of Neurology  
Wright State University Boonshoft  
School of Medicine  
USA

**Katherine H. Noe**

Department of Neurology  
Mayo Clinic  
USA

**Terence J. O'Brien**

Royal Melbourne Hospital  
Australia

**Alison M. Pack**

Neurological Institute  
Columbia University  
USA

**Philip N. Patsalos**

Department of Clinical and Experimental Epilepsy  
UCL Institute of Neurology  
UK

**Piero Perucca**

The Montreal Neurological Institute  
Canada

**Sandra J. Petty**

The Florey Institute of Neuroscience and Mental Health  
and  
Ormond College  
and  
Department of Medicine  
Royal Melbourne Hospital  
University of Melbourne  
Australia

**Michael Salzberg**

Department of Psychiatry  
St. Vincent's Hospital  
University of Melbourne  
Australia

**Joseph I. Sirven**

Department of Neurology  
Mayo Clinic  
USA

**Michael Smith**

Rush Epilepsy Center  
Rush University Medical Center  
USA

**Dee Snape**

Department of Public Health and Policy  
Institute of Psychology, Health and Society  
University of Liverpool  
UK

**Laura S. Snavely**

Department of Neurology, Penn State University  
Hershey, USA

**Cher Stephenson**

Stephenson Counseling LLC  
USA

**Erik K. St. Louis**

Department of Neurology  
Mayo Clinic  
USA

**Nancy J. Thompson**

Department of Behavioral Sciences and Health Education  
Rollins School of Public Health  
Emory University  
USA

**Lily H. Tran**

Department of Pediatrics and Neurology  
University of California at Irvine  
and  
Children's Hospital of Orange County  
USA

**Christopher Turnbull**

Melbourne Neuropsychiatry Centre  
University of Melbourne  
and  
Neuropsychiatry Unit  
Royal Melbourne Hospital  
Australia

**Frank J.E. Vajda**

Department of Medicine and Neuroscience  
University of Melbourne  
Royal Melbourne Hospital  
Australia

**Clemente Vega**

Division of Epilepsy and Clinical Neurophysiology  
Children's Hospital Boston and Harvard University  
USA

**Dennis Velakoulis**

Melbourne Neuropsychiatry Centre  
University of Melbourne  
and  
Neuropsychiatry Unit  
Royal Melbourne Hospital  
Australia

**John D. Wark**

Department of Medicine  
University of Melbourne  
and  
Bone & Mineral Medicine  
Royal Melbourne Hospital  
Australia

**Elizabeth Waterhouse**

Department of Neurology  
Virginia Commonwealth University School of Medicine  
USA

**Kristine Ziemba**

Department of Neurology  
Mayo Clinic  
USA

**Mary L. Zupanc**

Department of Pediatrics and Neurology  
University of California at Irvine  
and  
Children's Hospital of Orange County  
USA

# Preface

According to the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE), epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition [1]. This conceptual definition explicitly states that there is more to epilepsy than seizures. The ILAE and IBE conclude that for some people with epilepsy, “behavioural disturbances, such as interictal and postictal cognitive problems can be part of the epileptic condition...” and that “patients with epilepsy may suffer stigma, exclusion, restrictions, overprotection, and isolation, which also become part of the epileptic condition” [1].

Although it has long been known, increasing attention has recently been directed to the fact that comorbidities often add significantly to the burden of epilepsy, whether they are causative (e.g., cerebrovascular conditions or traumatic brain injuries causing epilepsy), resultant (caused by seizure, epilepsy, or its treatment), or related to a common cause underlying both the epilepsy and the comorbidity (e.g., learning disabilities or some psychiatric conditions). Such comorbidities not only add to the burden of epilepsy, but can also lead to poorer response to treatment with antiepileptic drugs, increased risk of adverse drug reactions, and even increased risk of death [2].

The theme of this book, “Epilepsy and The Interictal State: Co-Morbidities and Quality of Life,” is therefore very timely, and it addresses some of the most urgent issues for the successful management of people with epilepsy.

This volume takes a very broad approach to the Co-Morbidity and Quality of Life theme. Some emphasis is on cognitive impairments in epilepsy, including chapters on difficulties caused by neurodevelopmental

disorders and other co-morbidities, as well as on cognitive impairments caused by the treatment of epilepsy. Several chapters address other aspects of adverse effects of epilepsy therapies, ranging from idiosyncratic to dose/serum concentration-related, and even to second-generation effects on the unborn child. A particular strength of this book is that, in addition to identifying and describing these aspects of the burden of epilepsy, several chapters discuss ways to prevent, reduce, or manage adverse consequences of epilepsy and its treatment. Chapters on rehabilitation and the use of complementary medicine make this overview of possible interventions to improve everyday life for people with epilepsy most comprehensive. In conclusion, this book reminds us of the wider implications of the diagnosis of epilepsy, of the burden beyond seizures, and of our opportunities to assist in easing this burden. The editors have assembled world-renowned experts as authors to each of the 24 chapters, which contributes to making this book a most useful read for every physician involved in the management of people with epilepsy.

Torbjörn Tomson, MD, PhD  
Professor in Neurology and Epileptology  
Department of Clinical Neuroscience  
Karolinska Institutet  
Stockholm, Sweden

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## **SECTION I**

# Quality of life and the interictal state in epilepsy



## CHAPTER 1

# Quality of life in epilepsy: the key importance of the interictal state

David M. Ficker

*University of Cincinnati Neuroscience Institute Epilepsy Center, Department of Neurology, University of Cincinnati Academic Health Center, USA*

### Introduction

Quality of life (QOL) has become recognized as a critical concept in a wide range of disease states in medicine over the last several decades, especially in chronic medical conditions such as epilepsy. The traditional clinical measures used by clinicians in treating patients with epilepsy are seizure frequency and medication adverse effects. A patient with epilepsy is considered to be controlled when they are seizure-free and are having few or no adverse effects from their antiepileptic drugs (AEDs). Patients, however, may be more concerned about psychosocial issues such as driving, independence, and employment than about AED adverse effects or seizure unpredictability [1]. These aspects of QOL are infrequently assessed in routine clinical care. Although epilepsy is a disorder that only produces neurologic symptoms on an intermittent basis (i.e., only during the seizure), psychosocial problems, AED therapy, and side effects may be the major factors that a patient perceives as interfering with daily living. Other interictal factors have been explored as potential contributors to QOL and will be briefly reviewed here.

QOL is clearly subjective in nature and may be difficult to measure. In the simplest terms, QOL can be defined as how a patient feels and functions. There are three essential elements [2,3]: 1) physical health, 2) psychological health, and 3) social health. Physical health includes aspects such as daily function, general health, pain, endurance, and specific epilepsy-related variables such as seizure frequency, severity, and medication-related side effects. Psychological health

includes aspects such as emotional well-being, psychiatric and emotional health, self-esteem, and cognition. Social health includes aspects of relationships with friends and family, occupational status, and issues pertaining to independence.

### Tools for measuring QOL

Because QOL is difficult to quantify in everyday practice, research instruments have been developed with which to assess it. Measurement tools can be either generic or disease-specific.

Generic assessments such as the RAND 36-Item Health Survey [4] (also known as the SF-36) can be applied to many different patient populations and may allow for comparisons among different disease states. However, they may not measure important features in patients with epilepsy, such as fear of seizures or social embarrassment.

Epilepsy-specific measures of QOL have been developed over the past several years. The Quality of Life in Epilepsy (QOLIE) instruments were designed for use in a wide range of epilepsy patients, including those who with both benign and severe disease [3]. Three tools have been developed: QOLIE-89 [5], QOLIE-31 [6], and QOLIE-10 [7]. The QOLIE-89 contains 89 items in 17 scales, the QOLIE-31 contains 31 items in 7 scales, and the QOLIE-10 contains 10 items from the 7 QOLIE-31 scales and is intended as a screening tool. The scales represented in each survey are outlined in Table 1.1. All of the QOLIE inventories have been

**Table 1.1** Comparison of epilepsy-specific quality-of-life (QOL) tools.

Scale	QOLIE-89	QOLIE-31	QOLIE-10
Health perceptions	×		
Seizure worry	×	×	×
Physical function	×		
Role limitation, physical	×		
Role limitation, emotional	×		
Pain	×		
Overall QOL	×	×	×
Emotional well-being	×	×	×
Energy/fatigue	×	×	×
Attention/concentration	×	×	×
Memory	×		
Language	×		
Medication effects	×	×	×
Social function, work, driving	×	×	×
Social support	×		
Social isolation	×		
Health discouragement	×		

validated in studies of patients with epilepsy [5–7]. The questionnaires are simple to complete and have a standardized scoring system; however, they may be challenging to use in routine clinical practice. A QOL tool for newly diagnosed epilepsy patients (NEWQOL) has also been developed [8].

These tools have been used in many epilepsy QOL studies, and several important findings that impact the clinical practice of epilepsy have been reported. In particular, it seems that *interictal* factors rather than the ictal state have the greatest impact on QOL in epilepsy patients. While these findings may impact clinical practice, unfortunately interictal factors are often not routinely assessed in the clinic setting.

**Ictal factors: seizure frequency and severity**

It is relatively intuitive that seizures should affect QOL; large-scale surveys suggest that they have a negative impact. Seizure frequency, seizure type, and seizure severity each have an effect. A European study of 5000 epilepsy patients showed that those who experienced at least one seizure per month had poorer QOL than those who were seizure-free in the past year [9]. Another

study suggested that patients who had a minimum of six seizures over the previous 6 months had poorer QOL than those who had fewer seizures and those who were seizure-free [10]. In addition, patients who achieved seizure freedom had QOL similar to the general population [10]. A study analyzing different degrees of seizure control showed that QOL improved only when seizure freedom was attained, while lesser degrees of seizure reduction (i.e., 75–99%, 50–74%, or 0–50%) were not associated with improvement in QOL [11]. Recent seizures also seem to have a greater impact on QOL than more remote seizures [12] and have bearing on how patients with epilepsy prioritize the perceived impact of seizure control or medication adverse effects on QOL; in particular, patients who had recent seizures tended to be more sensitive toward medication adverse effects, while patients who had more remote seizures (but who had not experienced a recent seizure) were more concerned about seizure control [13]. Longer periods of seizure freedom were associated with better QOL in a cohort of over 600 people with epilepsy [14]. Seizure severity has also been shown to impact QOL in a number of studies [15–18]. Epilepsy surgery, especially when resulting in seizure freedom, results in improved QOL [19–21].

**Interictal factors**

While seizures and seizure severity may negatively impact QOL, when multivariate studies are performed there are other factors that have a greater effect. In particular, mood and medication adverse effects make a significant contribution to QOL.

The presence of medication adverse effects has been shown in several studies to negatively impact QOL. These studies utilized a standardized checklist of medication adverse effects: the Adverse Events Profile (AEP) [22]. In a cohort of 200 patients with epilepsy, higher AEP scores were associated with a worse QOL [23]. Use of the AEP in a randomized controlled trial resulted in improvements in QOL scores when clinicians were presented with AEP scores, compared to standard clinical practice without AEP review [24]. In this study, seizure frequency did not correlate with QOL but the presence of higher AEP scores was associated with a poorer QOL, suggesting the importance of interictal symptoms to QOL.

Comorbid mood disorders are very common in people with epilepsy [25], with both anxiety and depression being highly prevalent. Both depression and anxiety significantly impact QOL. A study of refractory epilepsy patients shows that depression is an important contributor to QOL, yet seizure-related factors are not [26]. Other studies suggest that depression and anxiety significantly impact QOL [27–30].

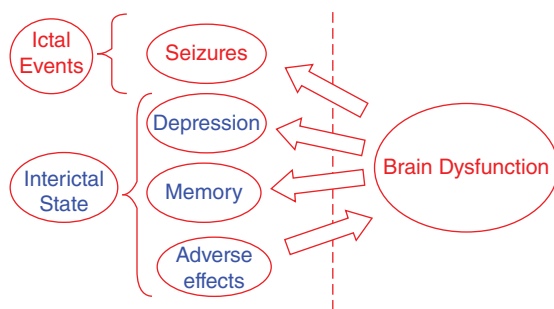
## Conclusion

Although it is important to assess ictal factors such as seizure frequency, severity, and recency in the clinic, interictal factors should be prioritized in order to maximize patient QOL. A conceptual model (Figure 1.1) can be used to elucidate the relationship between ictal and interictal factors in epilepsy QOL. There are many interrelated contributions; our traditional clinical assessments of seizure frequency and a cursory assessment of side effects may not be sufficient and other measures – including mood and more systematic and quantitative screening for adverse effects with validated tools such as the AEP – may be needed. In our epilepsy specialty clinics, we routinely include assessment of anxiety with the Generalized Anxiety Disorder 7-Item (GAD-7) scale [31] and of depression with the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) [32]. Use of these instruments may aid the clinician and patient in identifying otherwise subtle problems caused by mood, anxiety, or adverse

medication effects that have important bearing on QOL, leading to improved dialogue and proactive discussions that aid clinical decision-making in epilepsy care.

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**Figure 1.1** Conceptual model of quality of life (QOL) and epilepsy. It is crucial to address both ictal and interictal factors in epilepsy care; recent evidence has shown that interictal factors such as mood state, cognitive problems, and adverse medication effects have a crucial influence on epilepsy QOL.

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## CHAPTER 2

# Comorbidities in epilepsy: range and impact

J. Layne Moore<sup>1</sup> and John O. Elliott<sup>2</sup>

<sup>1</sup>*Department of Neurology, Wright State University Boonshoft School of Medicine, USA*

<sup>2</sup>*Department of Medical Education, Ohio Health Riverside Methodist Hospital and College of Social Work, Ohio State University, USA*

### Introduction

Although rendering patients “seizure-free” is the first goal of treating persons with epilepsy, many other factors affect their quality of life (QOL), including mental health and social, vocational, and somatic health issues [1].

The US government report *Healthy People 2010* sought to increase quality and years of healthy life and to diminish health disparities [2]. Recognition of comorbid conditions in persons with epilepsy may assist in selecting treatments and in identifying future goals and objectives for improving overall QOL.

A recent seminal article examining psychiatric and somatic comorbidities reported huge disparities in disease prevalence for persons with epilepsy in the United Kingdom [3]. Since this study, smaller-scale data have been reported from the United States in the 2003 California Health Interview Survey (CHIS).

### Psychosocial factors

Persons with epilepsy are at higher risk for symptoms of depression and anxiety than people suffering from many other chronic diseases [4]. Psychiatric disorders occur in persons with epilepsy almost twice as much as in the non-epilepsy population, including obsessive–compulsive disorder (OCD; rate ratio (RR) = 2.7), anxiety (RR = 2.2), depression (RR = 2.0), schizophrenia (RR = 3.8), and dementia (RR = 25.2) [3].

Persons with epilepsy and their families suffer from stigma that may impact how they are perceived and how

they view themselves [5]. Stigma may be worse when the diagnosis occurs early in life [6] and may be present even in incident epilepsy, especially in those with poor health or history of depression [7].

Patients who develop healthy attitudes are active and flexible, focusing on possibilities and planning how to handle negative emotions. In contrast, a “handicapped” group is passive and resigned to epilepsy in a negative way, is fearful of being exposed, and tends to focus on obstacles and negative emotions [8]. Persons with epilepsy report higher scores on measures of learned helplessness [9,10]. Persons with uncontrolled seizures are also prone to a greater sense of external locus of control [11].

However, an improved sense of self-efficacy (beliefs in one’s capabilities) to organize and execute action to produce attainments can assist persons with epilepsy in coping with their psychosocial difficulties [12]. Self-efficacy approaches may reduce disability and increase emotional well-being [13]. Such applications of neuropsychological and psychosocial interventions as treatment for epilepsy can also improve a person’s QOL [14].

Poor QOL is associated with greater utilization of medical resources (number of clinic visits, ER visits, and in-patient admissions) [15]. In one study, 90% of the variance in QOL was explained by a combination of disease severity, epilepsy self-efficacy, social support, and locus of control [16].

Socially isolated people are more likely to rate their health status as poor [17]. Poor community-level social connection results in poor self-rated health status [18]. Persons with epilepsy tend to lack an adequate

primary support group and have problems related to the social environment, education, occupation, housing, economic issues, and access to health care services.

### Social support

Unhealthy people are less likely to establish and maintain social relationships that provide social support [19]. An extensive body of literature suggests that poor social support is a major risk factor for morbidity and mortality, with statistical effect sizes comparable to established risk factors such as smoking, hypertension, high cholesterol, obesity, and physical activity [19].

A recent meta-analysis of 148 studies examining social relationships and mortality risk found a weighted average effect size odds ratio (OR) of 1.50 (95% CI 1.42–1.59), indicating a 50% increased likelihood of survival in persons with stronger integration in social networks providing social support [20]. This effect remained consistent across age, gender, initial health status, cause of death, and follow-up period.

In a 30-year longitudinal study from Finland, childhood onset seizures were found to have a long-term adverse impact on education, employment, marriage, and having children [21]. This negative impact was still present even when persons were seizure-free without medication for many years [21,22].

### Socioeconomic factors

Investigations have found that the incidence and prevalence of epilepsy in adults increases with socioeconomic deprivation [23–26]. Population studies from the United States show persons with a history of epilepsy report poorer health status, lower educational attainment, and lower household income compared to those without [27–29]. Persons with epilepsy are known to have significant difficulties in obtaining and maintaining employment [30]. These human capital factors improve health both directly and indirectly through work and economic conditions, psychosocial resources, and a healthy lifestyle [31]. For persons with epilepsy, limited education and employment impact health care access and environmental and lifestyle risk factors.

### Poverty

Poverty imposes constraints on the material conditions of everyday life through limitations on the

fundamentals of health: housing, good nutrition, and societal participation [32]. Material asset indicators such as home ownership are significantly associated with health outcomes after controlling for age, gender, and income [33].

People living in poverty who have difficulty paying for affordable housing and utility bills are less likely to have a usual source of care, more likely to postpone treatment, and more likely to use emergency-room services [34]. Persons with epilepsy living in poverty are half as likely to report taking medication for their seizures [35].

Income inadequacy adversely impacts the ability of persons with epilepsy to obtain not only medications but also basic resources such as food. Food insecurity is defined by the United States Department of Agriculture (USDA) as “when people do not have adequate physical, social, or economic access to sufficient, safe, and nutritious food that meets their dietary needs and food preferences for an active and healthy life” [36]. Adults in households with food insecurity are more likely to report poor or fair health status, as well as poor physical and mental health [37]. One recent Canadian study found persons with epilepsy were significantly more likely to report food insecurity [38].

Persons in poor environments experience significantly higher amounts of stress and poor mental health [39,40] and are more likely to adopt unhealthy coping behaviors such as smoking or drug and alcohol use [41].

### Somatic health issues

Somatic disorders are significantly increased in persons with epilepsy, including stroke (RR = 14.2), Alzheimer’s disease (RR = 39.8), Parkinson’s disease (RR = 2.5), migraine (RR = 1.6), heart disease (RR = 1.6), heart failure (RR = 2.4), diabetes (RR = 1.8), asthma (RR = 1.4), emphysema (RR = 2.9), peptic ulcer (RR = 2.2), and fractures (RR = 2.2) [3].

Based on the 2003 and 2005 CHIS data, persons with epilepsy experience a greater comorbid burden, especially for cardiovascular-related conditions [42]. In the 2005 CHIS, the prevalence ratios of many comorbid conditions remained significantly higher in persons with a history of epilepsy, including type II diabetes (OR = 1.4), asthma (OR = 1.7), high cholesterol (OR = 1.3), heart disease (OR = 1.6), stroke (OR = 4.3), arthritis (OR = 1.7), and cancer (OR = 1.4) [42]. The



Centers for Disease Control and Prevention (CDC) found similar results in their analysis of 19 US states surveyed about epilepsy in 2005 [27].

Persons with epilepsy are also at greater risk for premature death when compared to the general population. Several longitudinal studies from England found newly diagnosed persons with epilepsy had a 30–42% increase in mortality when compared to age- and gender-matched controls without epilepsy [43,44]. Persons with uncontrolled epilepsy had double the expected number of deaths [45], primarily to cerebrovascular disease, cancer, and respiratory diseases such as pneumonia and chronic obstructive pulmonary disease (COPD) [43–45].

### Physician–patient interactions

Clinicians are in a unique position to influence the health of persons with epilepsy. Unfortunately, time considerations and reimbursement issues are a significant barrier to their care. In general, medical literature has often reported poor communication between providers and patients [46]. The medical interview tends to be viewed as primarily a data-collection exercise, where there is typically an avoidance of psychological and social issues [47]. On average, physicians interrupt their patients within the first 18 seconds [48] of the interview and frequently overlook significant psychosocial issues [49].

A recent survey of persons with epilepsy in an out-patient setting revealed a selective gap between patients and their practitioners in understanding patients' concerns. Although there was overlap, patients were more concerned about life issues (memory and being a burden to others) and practitioners were more concerned about clinical issues (seizure activity and medication side effects). However well-meaning health care practitioners may be, attention should be spent on aligning their priorities with those of their patients [50].

Patient education has been shown to be effective in improving health outcomes such as reduction of medication needs, reduction of treatment duration and hospital stays, improvement in risk-reducing behavior, and reduction of risk factors [51]. Doctors who express doubts about their success in patient education tend to be pessimistic about their ability to influence their patients' lifestyles [52,53].

Physicians who practice healthy personal behaviors are reported to have more credibility and ability to counsel patients effectively about improving their own health behavior. In one study, neurologists rank among the least likely to provide prevention-related counseling or screening to their patients [54]. Improved exercise and dietary habits are complementary to each other and are typically of interest to patients in the clinical setting, potentially impacting the development or progression of comorbidities common in persons with epilepsy.

## Health behavior and lifestyle factors

### Sleep problems

Despite concern that persons with epilepsy should avoid sleep deprivation since as far back as Claudius Galen [55], persons with epilepsy are relatively sleepy compared to controls [56]. There are several likely causes for persons with epilepsy being excessively sleepy, including seizures, alteration of circadian rhythms, and the sedating effect of antiepileptic drugs (AEDs) [57]. Persons with epilepsy have more arousals and poorer sleep architecture [58]. They are also more likely to have other comorbidities that contribute to sleep deprivation, including obstructive sleep apnea [59].

### Smoking

Smoking is a significant concern, because studies have demonstrated a direct link with coronary artery disease, cancer, and stroke – the top three leading causes of death in the United States [60,61]. The 2003 and 2005 CHIS found significantly higher rates of smoking in persons with epilepsy [29,62]; these rates were confirmed in larger data from the Behavioral Risk Factor Surveillance System (BRFSS) [27].

### Exercise

A lack of understanding about epilepsy among many health professionals and sports instructors led to unnecessary restriction of physical activity [63]. Less than half of patients had ever talked to their doctor about physical activity [63]. In addition, overprotection by family members, understimulation, low self-esteem, isolation, depression, and anxiety are significant barriers to a healthy lifestyle [64]. The combination of these factors has likely had an untoward effect on mortality, morbidity, and QOL for persons with epilepsy.

Exercise has been shown to improve depressive symptoms in people who admit to symptoms of depression but would not meet criteria for a diagnosis [65]. This is particularly important when considering exercise advice for persons with epilepsy, since many would not meet diagnostic criteria for depression but are thought to suffer from an interictal dysphoric disorder [66]. Population surveys from the United States have consistently found that persons with epilepsy exercise much less frequently than those without epilepsy [27,62].

Clinically based studies of exercise in persons with epilepsy suggest patients benefit from a structured exercise program. A prospective, parallel, randomized controlled study evaluating the impact of 12 weeks of exercise on clinical, behavioral, and physiological outcomes in 28 patients with epilepsy found significant improvements in the overall Quality Of Life In Epilepsy-89 (QOLIE-89) score, especially in the physical function and energy/fatigue domains, without adverse impact on clinical outcomes such as antiepileptic drug concentrations or seizure activity [67]. Mood, as measured by the Profile of Mood States (POMS), was also significantly improved in the exercise group. Cardiovascular and resistance training significantly improved strength, peak oxygen consumption, endurance time, and lipid profiles. A 12-week exercise training program resulted in positive outcomes for patients with epilepsy [68].

Exercise participation recommendations should be reviewed with regard to seizure control, medications, proper diet, and rest, and AED levels should be monitored if necessary. If these aspects are taken into account, persons with epilepsy can participate in most types of physical activity, including some contact sports [69].

## Nutrition

Nutritional factors and poor diets may also contribute to the development of comorbidities in persons with epilepsy. In the United States, significant nutrient deficiencies (vitamins D, E, and K, folic acid, calcium, linoleic acid, and  $\alpha$ -linolenic acid) were found in more than 30% of children with intractable epilepsy through a recent analysis of the National Health and Nutrition Examination Survey (NHANES) for 2001–02 [70].

An examination of the 2005 CHIS found that persons with a history of epilepsy drank more soda and

consumed less salad than the non-epilepsy population [62]. However, the 2008 CDC report on epilepsy using the 2005 BRFSS data found persons with epilepsy reported consuming five servings of fruit and vegetables at the same rate as the non-epilepsy population [27].

## AEDs and nutritional factors

AEDs, the basis of all therapy for persons with epilepsy, have been found to deplete vitamins B6 and B2 [71–73] and lower blood folate levels [74–79]. Enzyme-inducing AEDs are known to cause vitamin D deficiency in persons with epilepsy [80,81]. Carbamazepine reduces blood levels of omega-3 fatty acids [82]. Other AEDs, particularly valproic acid, are also known to cause weight gain and increased carbohydrate cravings [83].

The therapeutic use of nutrition and nutritional supplementation is of interest in epilepsy [84]. However, due to methodological issues and a limited number of studies, there is presently little support [85] beyond the ketogenic diet [86] for such therapies in epilepsy.

## AEDs and comorbidity risk factors

Valproic acid, carbamazepine, or phenobarbital as long-term monotherapy have demonstrated atherogenic effects in children [87–89], although these effects are inconsistent [90]. Carbamazepine also increases atherogenic lipoproteins [91] and lipoprotein(a) in adult men [92]. However, carbamazepine has been found to increase high-density lipoproteins (HDL) in humans [93] and phenytoin has been found to reduce atherosclerosis by raising HDL in mice [94]. In children who complete AED treatment, lipids and lipoproteins typically return to normal 1 year after the end of treatment [95]. Additionally, carbamazepine and valproic acid can lead to significant weight gain, thereby increasing risk for metabolic syndrome and diabetes [96].

Since the 1980s, hypothyroidism has been associated with AED use. The mechanism is poorly understood but does not appear to be immune-mediated. Hypothyroidism may be more common in children and with the use of certain drugs, such as valproic acid, phenytoin, carbamazepine, and oxcarbazepine [97,98].

## Conclusion

Recognizing persons with epilepsy are at risk for many other problems allows physicians to anticipate and potentially mitigate these comorbidities. These topics will be expanded in the following chapters. Since persons with epilepsy develop many comorbid medical problems as a result of their own behaviors, patients should be regularly counseled about the importance of limiting weight gain through adequate dietary and exercise habits and about other factors such as avoidance of smoking. Appropriate counseling could reduce the risk of developing other future comorbidities, such as hypertension, vascular disease, and sleep apnea. Health care workers should also be vigilant for patient concerns that may not align with their own.

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