

EPILEPSY: BEING ILL IN MORE WAYS THAN ONE

Samuel Wiebe, MD, MSc, FRCPC,¹
and Dale C. Hesdorffer, PhD²

¹University of Calgary, Professor and Head, Division of Neurology, Foothills Medical Centre, Calgary, Alberta, Canada; ²Associate Professor of Clinical Epidemiology, Gertrude H. Sergievsky Center, Columbia University, New York, NY 10032, USA.

The majority of patients with epilepsy suffer from one or more psychiatric or somatic comorbid conditions, whose nature and prevalence vary with age and sociodemographic factors. In these patients, comorbid conditions have a major adverse effect on overall health and quality of life and substantially increase health care costs. Although there is an understanding of epidemiological aspects of the comorbidity of epilepsy, little is known about causal relationships, clinical interventions to prevent comorbidities, or the management of patients with multiple coexisting conditions. Both the effects of epilepsy therapies on comorbidities and the effects of comorbidities on the efficacy of epilepsy treatments warrant further study.

In chronic conditions, such as epilepsy, the coexistence of more than one illness in a patient is the rule rather than the exception. The coexistence of illnesses is referred to as *comorbidity* if the analysis focuses on an index condition (e.g., the comorbidity of epilepsy) or as *multimorbidity* if no particular condition is targeted (i.e., a group of conditions affecting an individual patient). Studies from developed countries, involving diverse epilepsy populations and using diverse methodologies, consistently report a higher prevalence of somatic and psychiatric conditions in individuals with epilepsy than in the general population. Men and women with epilepsy have a two- to five-fold increase in the occurrence of conditions, such as mi-

graine, cerebrovascular and cardiovascular disorders, gastrointestinal disorders, pulmonary disorders, dementia, chronic fatigue, mood disorders, anxiety, and personality disorders (1,2). The type and prevalence of conditions comorbid with epilepsy is age dependent and follows a similar distribution pattern to that of the general population; however, prevalence of comorbidities is higher for any given age group (2). For example, among patients with epilepsy, asthma is common in the young, while cardiovascular diseases and stroke are prevalent in older individuals—but both are more common than in the general population.

Patient-centered care of people with epilepsy requires an awareness of the many potential ways in which these patients are ill. Understanding comorbidity in epilepsy can guide therapeutic choices, impact outcomes, as well as shed light on causal factors and basic mechanisms of disease.

How Is Comorbidity Measured?

Clinicians and researchers are developing valid strategies to assess the magnitude of comorbidity and its impact on individual patients and on society. At a basic level, an evaluation of the prevalence of comorbid conditions can provide an estimation of the magnitude of the problem. In studies assessing the number of comorbid disease categories in neurological disorders, the median number of comorbid conditions is 11 for epilepsy and migraine, which is higher than for dementia (5 categories) or multiple sclerosis (3 categories), but lower than for stroke (21 categories) and depression (26 categories) (3). The high frequency of coexisting medical conditions is not unique to epilepsy or neurological disorders. In general practice studies, close to 60% of patients have two or more chronic comorbid conditions, and one-third have three or more comorbid conditions (4).

Comorbidity indices have been developed to assess the impact of a constellation of comorbid conditions on a variety of health outcome indicators, including quality of life, use of health resources, and survival. By reducing all coexisting illnesses to a single numeric score, indices stratify patients into groups with similar risks and allow comparisons among patient populations. While comorbidity indices do not gauge overall health or function, which are best captured by functional or quality-of-life scales, they yield an overall measure of the burden of an individual's mix of conditions, apart from and excluding the index condition. Importantly, no single comorbidity index predicts all relevant outcomes, and there is debate about the optimum indices for specific endpoints (e.g., survival, use of

Address correspondence to Samuel Wiebe, MD, Professor and Head, Division of Neurology, University of Calgary, Foothills Medical Centre, 1403 – 29 St NW Calgary, Alberta, Canada T2N 2T9. E-mail: swiebe@ucalgary.ca

Epilepsy Currents, Vol. 7, No. 6 (November/December) 2007 pp. 145–148
Blackwell Publishing, Inc.
© American Epilepsy Society

health resources, and quality of life). However, it is clear that the severity of illness is a key component in the assessment of comorbidity. Mounting evidence suggests that quality of life is more accurately predicted by comorbidity indices that incorporate measures of severity (5), even when severity is assessed with simple, self-rated, single questions (6). Metrics for severity of illness are not well developed in health measurement in general, and little is known about the severity of comorbid conditions or about the use of comorbidity indices in epilepsy. However, the importance of gauging severity of comorbid conditions in epilepsy is underscored by the seriousness of some of its comorbid conditions, such as suicidality and major depression.

Cause, Coincidence, or Consequence?

Comorbid conditions may precede, occur simultaneously with, or follow the diagnosis of epilepsy. The temporal occurrence of comorbid conditions is of importance to understanding causal associations and common or shared disease mechanisms. A review of reports of the temporal association of comorbid conditions with epilepsy reveals that a history of various conditions is associated with an increased risk for developing epilepsy. Among children, a history of attention deficit hyperactivity disorder, predominantly the inattentive type, is associated with an increased risk for epilepsy (7,8). Associations between migraine and epilepsy are bidirectional: migraine with aura is associated with an increased risk for developing epilepsy (9), while the risk for new-onset migraine is increased in people with a history of epilepsy (10); and, the prognosis of epilepsy is worse in the presence of migraine (10). Additionally, several population-based studies have shown that a history of major depression is associated with an increased risk for developing epilepsy (11–13). Clues regarding the underlying causes of these associations have been limited, yet it is unlikely that they are a mere coincidence; further clarification is needed to elucidate shared pathogenesis or shared genetic susceptibility.

Comorbidity and Quality of Life

Intuitively, the coexistence of more than one chronic condition should result in additive burdens on health. However, this may not always be the case. It is possible that the effects of comorbidity on quality of life may be multiplicative, additive, or negligible. In a systematic review of 45 studies assessing the impact of somatic or psychiatric comorbidities on overall quality of life in chronic conditions, 39 studies found that comorbidities were significantly associated with reduced quality of life (14). This review described close and complex interactions between somatic comorbidity, psychiatric comorbidity, and physiological measures, and found that somatic comorbidity affected mostly the physical aspects of quality of life, while psychiatric comorbidity affected both the physical and psychosocial aspects. These find-

ings underscore the importance of a comprehensive approach to managing comorbidity in epilepsy (15).

Few data exist to guide our understanding of the relative impact of various types of comorbidity on quality of life in epilepsy. However, it appears that a range of psychiatric comorbid conditions negatively impact quality of life to different degrees in patients with epilepsy; for instance, posttraumatic stress disorders and depression have the highest impact on quality of life, whereas schizophrenia has the lowest impact (16).

The Burden of Comorbidity

In a world of increasing health care costs and growing awareness of global health issues, planning of health services and allocation of scarce health resources requires an understanding of the relative burden imposed by various illnesses. At the global level, the World Health Organization recognizes the importance of identifying *dependent* comorbidity; that is, identifying when the probability of having a pair of diseases is greater than the product of the probability of the occurrence of either disease alone. Such data allow for more precise calculations of health state levels, life expectancy, and overall burden of disease associated with specific conditions (16), and they guide prioritization of targets for public health initiatives. At the level of individual studies on burden of disease, a cogent distinction between costs associated with a single clinical condition and those pertaining to comorbid conditions would be valuable. This approach would allow for a meaningful interpretation of the cost of an illness and cost–outcome estimates.

In general, the unadjusted annual median costs of medical comorbid conditions are similar among patients with chronic diseases in the United States adult population, ranging between \$1,100 and \$1,500. However, annual adjusted costs increase exponentially as comorbidity increases. Patients with mild-to-moderate comorbidity (Charlson Index scores ≥ 2) account for 26% of the population but for 50% of the overall costs (17). This finding underscores the overwhelming impact of comorbidity on the economic burden of a disease. No studies have addressed the economic burden of comorbidity in epilepsy, but the same general principles are likely to apply.

Sociodemographic factors also have an important influence on the type and severity of chronic comorbidities. For example, in developing countries, the prevalence of infectious and parasitic comorbidities is much higher, and access to care is more limited than in developed countries. These factors are important because epidemiological data on the comorbidity of epilepsy derive largely from developed countries. However, low socioeconomic status may influence the number, type, severity, and impact of comorbid conditions even in the developed world (18). Much needs to be learned about the comorbidity

of epilepsy both in developing countries and in diverse sociodemographic settings of developed countries.

How Can Comorbidity Be Managed for Patients with Epilepsy?

A recent systematic review demonstrates that over 70% of the published studies on comorbidity are descriptive and epidemiological in nature, and most deal with patient populations over 60 years old. Only 6% of the studies focus on experimental interventions to prevent or treat comorbidity (19). Commentators have pointed to the lack of evidence-based guidance regarding the management of patients with coexisting conditions. Clinical practice guidelines typically focus on single conditions and do not discuss the appropriateness of the recommendations for patients with comorbidities (20). The jury is still out in regard to adequacy of care for patients suffering from multiple conditions. Some studies suggest that the majority of patients with comorbidities do not receive optimum care (4) or that comorbidities are underdiagnosed. Other research indicates that individuals with multiple comorbidities receive better medical care than those without them. For example, quality-of-care indicators were fulfilled in 59% of elderly individuals with five to six coexisting conditions, as compared to 47% of those with fewer conditions—a statistically significant difference (21). It also is possible that certain epilepsy comorbidities share an underlying etiology and that treating them will reduce the severity of the seizure disorder, as has been proposed by some investigators for mood and anxiety disorders concurrent with epilepsy. Conversely, successful treatment of seizures may reduce the severity of certain comorbidities, such as mood and anxiety disorders.

Although stratification and subgroup analyses for prognostic variables are common in clinical intervention trials, few trials give specific consideration to the interaction between comorbidities and the intervention, let alone to their directionality. Not uncommonly, patients with important comorbid conditions are excluded from participation in clinical trials, further impeding the applicability of the evidence to large segments of patients.

Multimorbidity is common in medicine. In epilepsy, comorbidity is the rule rather than the exception. However, there is a lack of sufficient information about the severity of these comorbidities, the direction of causality with epilepsy, their full impact on individual patients, and their frequency in diverse populations. The effects of existing and new epilepsy therapies on comorbidities need to be explored, as do the effects of comorbidities on the efficacy of treatments for epilepsy. Trials are needed that include patients with comorbidities and then provide explicit data about outcomes in relation to comorbidities. Finally, it will be important to assess the effect of interventions for epilepsy on comorbid conditions as well as the effect of in-

terventions for comorbid conditions on key epilepsy outcomes, such as seizures, quality of life, and mortality.

References

- Gaitatzis A, Carroll K, Majeed A, Sander W. The epidemiology of the comorbidity of epilepsy in the general population. *Epilepsia* 2004;45:1613–1622.
- Tellez-Zenteno J, Soofi A, Wiebe S. Age related somatic comorbidity in people with epilepsy in the general population. *Neurology* 2007; 68(Suppl.) A359.
- Nuyen J, Schellevis FG, Satariano WA, Spreuwenberg PM, Birkner MD, van den Bos GA, Groenewegen PP. Comorbidity was associated with neurologic and psychiatric diseases: a general practice-based controlled study. *J Clin Epidemiol* 2006;59:1274–1284.
- Kahn LS, Fox CH, Olawaiye A, Servoss TJ, Lean-Plunkett E. Facilitating quality improvement in physician management of comorbid chronic disease in an urban minority practice. *J Natl Med Assoc* 2007;99:377–383.
- Fortin M, Hudon C, Dubois MF, Almirall J, Lapointe L, Soubhi H. Comparative assessment of three different indices of multimorbidity for studies on health-related quality of life. *Health Qual Life Outcomes* 2005;3:74.
- Bayliss EA, Ellis JL, Steiner JF. Subjective assessments of comorbidity correlate with quality of life health outcomes: initial validation of a comorbidity assessment instrument. *Health Qual Life Outcomes* 2005;3:51.
- Austin JK, Harezlak J, Dunn DW, Huster GA, Rose DF, Ambrosius WT. Behavior problems in children before first recognized seizures. *Pediatrics* 2001;107:115–122.
- Hesdorffer DC, Ludvigsson P, Olafsson E, Gudmundsson G, Kjartansson O, Hauser WA. ADHD as a risk factor for incident unprovoked seizures and epilepsy in children. *Arch Gen Psychiatry* 2004;61:731–736.
- Ludvigsson P, Hesdorffer D, Olafsson E, Kjartansson O, Hauser WA. Migraine with aura is a risk factor for unprovoked seizures in children. *Ann Neurol* 2006;59:210–213.
- Ottman R, Lipton RB. Comorbidity of migraine and epilepsy. *Neurology* 1994;44:2105–2110.
- Forsgren L, Nystrom L. An incident case-referent study of epileptic seizures in adults. *Epilepsy Res* 1990;6:66–81.
- Hesdorffer DC, Hauser WA, Annegers JF, Cascino G. Major depression is a risk factor for seizures in older adults. *Ann Neurol* 2000;47:246–249.
- Hesdorffer DC, Hauser WA, Olafsson E, Ludvigsson P, Kjartansson O. Depression and suicide attempt as risk factors for incident unprovoked seizures. *Ann Neurol* 2006;59:35–41.
- Baumeister H, Balke K, Harter M. Psychiatric and somatic comorbidities are negatively associated with quality of life in physically ill patients. *J Clin Epidemiol* 2005;58:1090–1100.
- Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *Gen Hosp Psychiatry* 2007;29:147–155.
- Mathers CD, Iburg KM, Begg S. Adjusting for dependent comorbidity in the calculation of healthy life expectancy. *Popul Health Metr* 2006;4:4.
- Charlson M, Charlson RE, Briggs W, Hollenberg J. Can disease management target patients most likely to generate high costs?

- The impact of comorbidity. *J Gen Intern Med* 2007;22:464–469.
18. Schrijvers CT, Coebergh JW, Mackenbach JP. Socioeconomic status and comorbidity among newly diagnosed cancer patients. *Cancer* 1997;80:1482–1488.
 19. Fortin M, Lapointe L, Hudon C, Vanasse A. Multimorbidity is common to family practice: is it commonly researched? *Can Fam Physician* 2005;51:244–245.
 20. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA* 2005;294:716–724.
 21. Min LC, Wenger NS, Fung C, Chang JT, Ganz DA, Higashi T, Kamberg CJ, Maclean CH, Roth CP, Solomon DH, Young RT, Reuben DB. Multimorbidity is associated with better quality of care among vulnerable elders. *Med Care* 2007;45:480–488.