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<p>This article reviews evidence of quality of life (QOL) determinants in people affected by epilepsy, including detractors and promoters. Emerging factors of particular significance for QOL are highlighted, including seizure frequency, medication side effects, psychological comorbidity, and stigma and discrimination. This article also examines the role of resilience, interpreted in its widest sense, for promoting good QOL, even in the presence of poorly controlled seizures. The importance of addressing both clinical and wider psychosocial issues is highlighted and some possible directions for future research into QOL in epilepsy are suggested.</p>	
<b>Depression and Epilepsy: A Review of Multiple Facets of Their Close Relation</b>	<b>865</b>
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<p>Depressive disorders are the most frequent psychiatric comorbidity in patients with epilepsy (PWE). Although they are typically considered a psychiatric disorder, ample data suggest that depressive disorders are a neurologic disorder with psychiatric clinical manifestations. Patients with epilepsy whose seizures originate in temporal and frontal lobes have the highest prevalence of comorbid depressive disorders. Not only are patients with epilepsy at higher risk of developing depression but also patients with depression are at higher risk of developing epilepsy. This article reviews these data, the clinical manifestations of depressive disorders in PWE, and their significant impact on the suicidal risk and quality of life.</p>	
<b>The Emerging Architecture of Neuropsychological Impairment in Epilepsy</b>	<b>881</b>
Bruce P. Hermann, Jack J. Lin, Jana E. Jones, and Michael Seidenberg	
<p>A new literature is now under way, one linking cognitive abnormalities directly to indices of structural, functional, metabolic, and other neurobiologic markers of cerebral integrity, independent of their association with clinical epilepsy characteristics. These trends are reviewed in this article. The focus is on temporal lobe epilepsy (TLE) as a model with which to address the core points because this form of localization-related epilepsy has been very carefully studied from both a cognitive and imaging standpoint. Some pertinent historical issues are touched on first, followed by more detailed reviews of the cognitive and neuroimaging abnormalities that have</p>	

been found in TLE, followed by an overview of studies examining direct structure-function relationships in TLE and other epilepsies.

**The Etiology of Psychogenic Non-Epileptic Seizures: Toward a Biopsychosocial Model** 909

Markus Reuber

Psychogenic non-epileptic seizures (PNES) are one of the most common differential diagnoses of epilepsy. PNES are poorly understood and often sub-optimally treated. This article summarizes current knowledge about the etiology of PNES. Through describing the interactions of predisposing, precipitating, perpetuating, and triggering factors, an integrated biopsychosocial model of a complex disorder is developed. PNES emerge as a dissociative response to a range of different stressors in vulnerable individuals. Once established, maintaining factors turn a temporary disturbance into a chronically disabling disorder.

**Predicting Seizures: A Behavioral Approach** 925

Sheryl R. Haut and Richard B. Lipton

This article reviews the clinical evidence for seizure prediction. The epilepsy cycle is considered, including the interictal, preictal, ictal, and postictal phases. Evidence suggesting that the preictal phase can sometimes be identified based on neurophysiologic signals, premonitory features, the presence of trigger factors, or self-report is discussed. Diary studies have shown that seizures are not randomly distributed in time and that a subgroup of persons with epilepsy can predict an impending seizure. Paper diary data and preliminary analysis of electronic diary data suggest that seizure prediction is feasible.

**Hormonal Aspects of Epilepsy** 941

Page B. Pennell

The interactions between hormones, epilepsy, and the medications used to treat epilepsy are complex, with tri-directional interactions which affect both men and women in various ways. Abnormalities of baseline endocrine status occur more commonly in people with epilepsy, and are most often described for the sex steroid hormone axis. Common symptoms include sexual dysfunction, decreased fertility, premature menopause, and polycystic ovarian syndrome. Antiepileptic drugs (AEDs) and hormones have a bidirectional interaction, with a decrease in the efficacy of hormonal contraceptive agents with some AEDs and a decrease in the concentration and efficacy of other AEDs with hormonal contraceptives. Endogenous hormones can influence seizure severity and frequency, resulting in catamenial patterns of epilepsy. However, this knowledge can be used to develop hormonal strategies to improve seizure control in people with epilepsy.

**Selection of Antiepileptic Drugs in Adults** 967

Linda J. Stephen and Martin J. Brodie

Epilepsy affects approximately 50 million people worldwide, with an annual incidence of 50 to 70 cases per 100,000 population. The condition

can strike at any time of life, with an immediate impact on everyday activities and routine. Key to optimal management is swift referral to an epilepsy specialist, appropriate investigation, and timely institution of antiepileptic drug therapy. In the past 20 years, the explosion of 13 new agents into the marketplace has greatly increased the potential for therapeutic intervention. This article explores the rationale for treatment selection in adults with epilepsy.

### **Teratogenic Effects of Antiepileptic Medications**

993

Torbjörn Tomson and Dina Battino

During the last few years epilepsy and pregnancy registries and other large scale observational studies have provided new information on the teratogenic effects of the most frequently used antiepileptic drugs (AEDs). The prevalence of major congenital malformations associated with exposure to carbamazepine or lamotrigine appears to be only marginally increased from the expected, while malformation rates with valproate have been reported to be 2 to 4 times higher. Recent studies also suggest that compared with carbamazepine, lamotrigine and phenytoin, exposure to valproate *in utero* may be associated with poorer postnatal cognitive development. However, adverse outcomes with valproate appear to be dose-related, and doses below 800-1,000 mg/day might not be associated with worse outcome than with other AEDs. Information on the teratogenic potential of other newer generation AEDs than lamotrigine is still insufficient.

### **Identification of Pharmacoresistant Epilepsy**

1003

Anne T. Berg

There is no single definition of pharmacoresistant (intractable, refractory) epilepsy. Prospective identification of pharmacoresistance is complicated by the variability of its appearance across different types of epilepsy and the variability of seizure control within a given patient over time. Failure of informative trials of two appropriate antiepileptic drugs has been recommended as a threshold that should trigger referral for evaluation at a comprehensive epilepsy center. Maximizing seizure control is imperative for reducing the risks and consequences of epilepsy, including the cognitive and psychiatric comorbidities and even sudden death.

### **Localization in Epilepsy**

1015

Dimitris G. Placantonakis and Theodore H. Schwartz

Pharmacologic therapy represents the first line of treatment of epilepsy and is effective in most patients. However, about 20% to 30% of cases develop intractable seizures that cannot be controlled by medication alone. In such cases, surgical intervention is considered for therapeutic, often curative purposes. Dynamic spatiotemporal variability in the epileptic focus renders seizure localization a challenge to the clinician. Many diagnostic modalities have been developed to identify different aspects of the

epileptic focus. Older techniques are being increasingly supplemented by a variety of anatomic and functional imaging modalities that can help clarify discrepancies. Invasive electroencephalography remains the gold standard for identifying epileptic foci and guiding the surgeon to successful resections.

### **Therapeutic Brain Stimulation for Epilepsy**

1031

Juliana Lockman and Robert S. Fisher

Deep brain stimulation (DBS) for epilepsy is a functional therapy that avoids many of the adverse effects associated with antiepileptic drug therapy and resective brain surgery. DBS is a relatively new therapy, and only recently has controlled evidence shown its efficacy. This article concentrates on clinical studies of DBS for epilepsy.

### **Advances on the Genetics of Mendelian Idiopathic Epilepsies**

1041

Stephanie Baulac and Michel Baulac

Genetic factors play an increasingly recognized role in idiopathic epilepsies. Since 1995, positional cloning strategies in multi-generational families with autosomal dominant transmission have revealed 11 genes (*KCNQ2*, *KCNQ3*, *CHRNA4*, *CHRNA2*, *CHRN2*, *SCN1B*, *SCN1A*, *SCN2A*, *GABRG2*, *GABRA1*, and *LG11*) and numerous loci for febrile seizures and epilepsies. To date, all genes with the exception of *LG11* (leucine-rich glioma inactivated 1), encode neuronal ion channel or neurotransmitter receptor subunits. Molecular approaches have revealed great genetic heterogeneity, with the vast majority of genes remaining to be identified. One of the major challenges is now to understand phenotype–genotype correlations. This review focuses on the current knowledge on the molecular basis of these rare Mendelian autosomal dominant forms of idiopathic epilepsies.

### **Sudden Unexpected Death in Epilepsy (SUDEP): Update and Reflections**

1063

Lina Nashef and Philippe Ryvlin

This article addresses aspects of sudden unexpected death in epilepsy, reflecting on current knowledge and questions that need answers to quantify, monitor, and reduce risk. A brief overview is followed by a discussion of definitions, drug treatment, genetic susceptibility, mechanisms in relation to seizure monitoring units and supervision, with some suggestions for the way forward.

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