



Epilepsy therapy in 2010

“The articles in this issue of Therapy address advances in a broad range of therapies for people with epilepsy. The plethora of medications and other treatment options, including surgery and brain stimulation, testifies to the lack of a ‘magic bullet’ for seizure control.”

Epilepsy is a chronic neurologic condition, characterized by recurrent unprovoked seizures that affect over 2 million people in the USA [1] and 50 million worldwide [2]. Annual direct and indirect costs total at least US\$12.5 billion in the USA [1]. Other costs to the individual with epilepsy, such as physical, psychological and social costs, are more difficult to quantify but no less important. Compared with the general population, mortality is increased 2–3 times from accidents, suicide, sudden unexplained death from epilepsy and other causes [3,4]. This issue of *Therapy* provides an update of epilepsy treatment, focusing on advances in seizure control and quality of life.

Medications remain the mainstay of therapy. Approximately 20 drugs are currently available to treat epilepsy, 11 of these have been approved by the US FDA since 1993 [5]. Extended-release formulations, designed to limit adverse effects and improve compliance, have also become available for several widely used antiepileptic drugs. Drug selection relies on the classification of each patient’s epilepsy syndrome, seizure type, comorbidities, concurrent medications, adverse physical and neuropsychiatric medication effects, consideration of teratogenicity, cost, and other factors [5].

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All currently available medications for epilepsy may be categorized as symptomatic or anti-seizure treatments. In this respect, the treatment of epilepsy is similar to other neurologic diseases, such as Alzheimer’s and Parkinson’s diseases, where medications may improve symptoms, but do not attack the underlying pathophysiology.

Efforts to develop antiepileptogenic drugs that might ‘cure’ epilepsy or, in the case of an etiologic event, such as head trauma, prevent epilepsy from developing, are ongoing.

Despite the multiple medications available, approximately 30% of people with epilepsy suffer intractable, uncontrolled or refractory epilepsy [6]. Since this estimate in 2000, five new drugs have received FDA approval. Although patients occasionally become seizure free when trying a novel drug, the number of patients with refractory epilepsy remains surprisingly high.

An additional factor affecting seizure control is poor medication adherence, which occurs in 30–50% of adult patients [7]. Adherence in certain populations, such as adolescents, may be particularly problematic [8].

Even in childhood absence epilepsy – a so-called ‘benign’ epilepsy – a recent comparative trial of three commonly used drugs (ethosuximide, lamotrigine and valproic acid) revealed that more than 40% of children were deemed treatment failures on even the most effective therapy [9]. Ethosuximide and valproate were demonstrated to be significantly more effective than lamotrigine. Furthermore, attentional dysfunction was less common with ethosuximide than valproate [9]. These results challenge the hypothesis that new drugs are superior to older ones [10]. Pharmacogenomics, which promises to guide medication choice based on underlying genetic defects and defined flawed cellular mechanisms is not yet applicable in the epilepsy clinic for the vast majority of patients [10]. For the physician prescribing an antiseizure drug, individualization of therapy for the particular patient, relying on all the options available remains the optimal approach.

To improve research and communication on this topic, the definition of ‘drug-resistant epilepsy’, has been formally proposed as “failure of adequate trials of two tolerated and appropriately



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chosen and used AED [antiepileptic drug] schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" [11]. Patients with drug-resistant epilepsy may be considered for more invasive therapy, such as vagus-nerve stimulation (VNS), other brain stimulation, epilepsy surgery and other specialized therapies.

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Epilepsy surgery is a venerable, yet underutilized, approach for patients with drug-resistant epilepsy [12]. Surgical treatment offers the possibility of seizure freedom for patients with drug-resistant epilepsy and should not be overlooked as a treatment option. In this issue, Chakraborty and Rutka describe modern applications of magnetoencephalography, neuroimaging with 3-Tesla MRI, invasive EEG recording and brain mapping that have improved preoperative localization of the epileptogenic zone and eloquent cortex in preparation for seizure surgery [13]. The authors also provide a succinct overview of the different types of resective and nonresective surgical procedures. In a special interview, personal and global perspectives on epilepsy surgery are offered by Engel, one of the most experienced and prolific clinical researchers in the field [14].

For patients with drug-resistant epilepsy not amenable to surgery, electrical brain stimulation offers another modality for seizure reduction. The VNS, FDA approved in 1997, has evolved into a standard therapy for people with epilepsy, with over 40,000 stimulators implanted worldwide [102]. The success of VNS, deep-brain stimulation for Parkinson's disease and steady advances in biomedical engineering have led to an increased number of neuromodulating options for epilepsy treatment, including various targets for deep-brain stimulation, transcranial magnetic stimulation and responsive neurostimulation. A multicenter, randomized, double-blind prospective trial of stimulation of bilateral anterior nuclei of the thalamus in 110 subjects demonstrated significant seizure reduction in patients with temporal-lobe epilepsy [15]. An FDA advisory committee has recommended approval, and final action is pending [103]. Trials of Neuropace's

responsive neurostimulation (RNS[®]) System have been encouraging and also await FDA approval [104]. Widdess-Walsh *et al.* review our current knowledge of epilepsy treatment with neurostimulation [16].

Drug-resistant epilepsy in childhood may impede a child's academic and social development owing to recurrent seizures and adverse effects of antiepileptic drugs. McCoy and Benbadis review the psychosocial impact of drug-resistant epilepsy in children and emphasize the benefits of early referral to a specialized epilepsy center [17]. The authors propose a structured approach to the diagnosis and presurgical evaluation of children with drug-resistant epilepsy. Options for children with drug-resistant epilepsy who are not surgical candidates, such as VNS, the ketogenic and other diets, and additional pharmacotherapy are also discussed.

Post-traumatic epilepsy is responsible for approximately 5% of cases of epilepsy. Current military conflicts are substantially adding to the population of people with traumatic brain injury at risk of epilepsy, enhancing the timeliness of this topic. The delayed onset of epilepsy after traumatic brain injury offers a unique research model regarding the factors that contribute to epileptogenesis. Verellen and Cavazos summarize definitions, predictors of epilepsy and treatment of post-traumatic epilepsy [18].

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Although seizure control remains the number one goal of epilepsy treatment, the effect of medications and other therapies on quality of life, as well as an increased prevalence of comorbid neuropsychiatric issues, must also be addressed. Alsaadi reviews the increased risk of psychiatric disorders associated with epilepsy, their possible etiologic basis and the significant impact on health-related quality of life [19]. Alsaadi stresses the importance of depression screening and treatment, as well as heightened awareness of the risk of suicide in people with epilepsy.

Women with epilepsy present multiple unique management issues that have recently been reviewed in three American Academy Practice Parameters [20–22]. In addition to considering

seizure type and the adverse event profile of anti-epileptic drugs, the possibility of teratogenicity looms as a major concern for the approximately 500,000 women in the USA of childbearing age [21]. Tornes and Harden summarize the emerging data from several antiepileptic drug pregnancy registries that have recently become available, to inform our treatment choices and decrease the risk of birth defects in the offspring of women with epilepsy [23].

Ultimately, the treatment of epilepsy is designed to improve a patient's quality of life, which, in addition to seizure control, includes cognitive, physical, social, sensory and emotional functioning. Nowinski *et al.* describe two NIH-funded initiatives, Neuro-QOL and the NIH Toolbox for the Assessment of Neurological and Behavioral Function, which are developing brief quality of life measurement tools for people with neurologic diseases including epilepsy [24]. In the near future, availability of both of these assessment tools with computerized scoring will facilitate clinical research and may encourage quality of life evaluation within the time constraints of the epilepsy clinic.

Conclusion

The articles in this issue of *Therapy* address advances in a broad range of therapies for people with epilepsy. The plethora of medications and other treatment options, including surgery and brain stimulation, testifies to the lack of a 'magic bullet' for seizure control. For optimal success, treatment must be individualized according to different seizure types and syndromes, as well as adverse drug effects on behavior, cognition and teratogenicity. The use of screening

tools for depression will improve detection of this under-recognized and undertreated comorbid condition.

Refinements in surgical techniques and development of more innovative neuro-stimulating devices continue to improve patient outcomes. Increased patient and physician education regarding epilepsy treatment is more important than ever, as sophisticated epilepsy treatment becomes more widespread and new treatments are offered.

As our understanding of epilepsy increases, newer medications will, ultimately, become more targeted and effective. Future research into the mechanisms of epileptogenesis may someday lead to the discovery of true antiepileptogenic drugs, which may prevent the development of 'a condition of recurrent seizures' in people at risk, such as those with genetic predisposition or post-traumatic injury, and even eliminate epilepsy once it has begun. In the meantime, proper application of our current knowledge regarding diagnosis, drug selection, and utilization of surgical, electrical and other alternative therapies offers many patients the opportunity of fewer seizures and improved quality of life.

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Bibliography

- Begley CE, Famulari M, Annegers JF *et al.*: The cost of epilepsy in the United States: an estimate from population-based clinical and survey data. *Epilepsia* 41(3), 342–351 (2000).
- Leonardi M, Ustun TB: The global burden of epilepsy. *Epilepsia* 43(Suppl. 6), 21–25 (2002).
- Cockerell OC: The mortality of epilepsy. *Curr. Opin. Neurol.* 9(2), 93–96 (1996).
- Nei M, Ho RT, Abou-Khalil BWA *et al.*: EEG and ECG in sudden unexplained death in epilepsy. *Epilepsia* 45(4), 338–345 (2004).
- Chong DJ, Bazil CW: Update on anticonvulsant drugs. *Curr. Neurol. Neurosci. Rep.* 10, 308–318 (2010).
- Kwan P, Brodie MJ: Early identification of refractory epilepsy. *N. Engl. J. Med.* 342(5), 314–319 (2000).
- Brown I, Sheeran P, Reuber M: Enhancing antiepileptic drug adherence: a randomized controlled trial. *Epilepsy Behav.* 16(4), 634–639 (2009).
- Asato MR, Manjunath R, Sheth RD *et al.*: Adolescent and caregiver experiences with epilepsy. *J. Child Neurol.* 24(5), 562–571 (2009).
- Glauser TA, Cnaan A, Shinnar S *et al.*: Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. *N. Engl. J. Med.* 362, 790–799 (2010).
- Vining EPG: Ethosuximide in childhood absence epilepsy – older and better. *N. Engl. J. Med.* 362, 843–845 (2010).
- Kwan P, Arzimanoglou A, Berg AT *et al.*: Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 51(6), 1069–1077 (2010).
- Engel J, Wiebe S, French J *et al.*: Practice parameter: temporal lobe and localized neocortical resections for epilepsy. *Neurology* 60, 538–547 (2003).
- Chakraborty A, Rutka JT: Surgical approaches to epilepsy. *Therapy* 7(5), 467–479 (2010).
- Engel J Jr: The importance of surgery for epilepsy. *Therapy* 7(5), 453–457 (2010).
- Fisher R, Salanova V, Witt T *et al.*: Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* 51(5), 899–908 (2010).

- 16 Widdess-Walsh P, Kellinghaus C, Geller E, Bösebeck F, Schuele S, Loddenkemper T: Efficacy of electrical brain stimulation in epilepsy. *Therapy* 7(5), 481–496 (2010).
- 17 McCoy B, Benbadis SR: Approach to refractory childhood seizures. *Therapy* 7(5), 497–506 (2010).
- 18 Verellen RM, Cavazos JE: Post-traumatic epilepsy: an overview. *Therapy* 7(5), 527–531 (2010).
- 19 Alsaadi T: Neuropsychiatric issues in patients with epilepsy: focus on depression. *Therapy* 7(5), 507–515 (2010).
- 20 Harden CL, Hopp J, Ting TY *et al.*: 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, 126–132 (2009).
- 21 Harden CL, Meador KJ, Pennell PB *et al.*: 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, 133–141 (2009).
- 22 Harden CL, Pennell PB, Koppell BS *et al.*: 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* 73, 142–149 (2009).
- 23 Tornes L, Harden CL: Antiepileptic drug pregnancy registries: do the latest findings concur? *Therapy* 7(5), 517–526 (2010).
- 24 Nowinski CJ, Victorson D, Cavazos JE, Gershon R, Cella D: Neuro-QOL and the NIH Toolbox: implications for epilepsy. *Therapy* 7(5), 533–540 (2010).

■ Websites

- 101 Mancinelli L, Cronin M, Sadee W: Pharmacogenomics: the promise of personalized medicine. *AAPS PharmSci.* 2(1), Article 4 (2000)
www.aapspharmsci.org
- 102 Cyberonics
www.cyberonics.com
- 103 US FDA
www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM209700.pdf
- 104 Neuropace
www.neuropace.com