EDITORIAL COMMENT

In this issue of Epilepsia, we present the next in our series of review, opinion, and commentary (pp. 1277–1288). Other such series, published in Gray Matters over the past couple of years, include discussions about: ethical dimensions of epilepsy genetics [2006, 47(10):1747–1756]; internet research [2007, 48(7):1415–1424]; drug resistance [2007, 48(12):2369–2374]; SCN1A mutation and sudden unexplained death in epilepsy (SUDEP) [2008, 49(2):360–369]; and Wada testing [2008-49(4):715–727]. One reader has pointed out that we have not explained the format or purpose of these series, and so we have now added a section heading to clarify our intent. In these series, we publish a lead paper followed by commentaries that have been invited by the editors specifically to put forward different views. In commissioning such commentary, we hope to encourage discussion and debate that will lead to further research and elucidation of these still controversial issues. We hope this initiative is of interest to readers, and we invite readers to suggest new topic areas for debate within the pages of Epilepsia.

CONTROVERSIAL TOPICS IN EPILEPSY

[In this section, we present a lead paper – a workshop report – followed by a pair of comment articles that have been invited by the editors. Our goal is to present different or opposing views on topical issues. Articles and comment are commissioned in the spirit of encouraging discussion and debate in a format that will stimulate thought and further research.]

The drug treatment of status epilepticus in Europe: Consensus document from a workshop at the first London Colloquium on Status Epilepticus

This document summarizes the conclusions of a workshop of European clinicians held in conjunction with the first London Colloquium on Status Epilepticus, in April 2007. The purpose of the workshop was to outline options for treatment of the various forms of status epilepticus (SE) and to identify regulatory and medical aspects which require action, in the European context. The document provides: (1) suggestions for action to improve knowledge and practice in relation to SE (shaded in gray) and (2) options for treatment of various forms of SE (shaded in green).

This document was approved by the Commission on European Affairs of the International League Against Epilepsy (ILAE).

This is not a guideline document, but summarizes treatment options in an area characterized by a lack of randomized controlled trials or indeed other large studies. The various forms of SE are a significant health problem and often need urgent expert therapy to optimize outcome.

The availability of intravenous antiepileptic drugs (AEDS) used in this condition, and their licensing status, varies across European countries, and this variation is to the detriment of patients (Annex 1). There is widespread use of nonlicensed drugs, which is unsatisfactory, and in some areas the treatment and protocols vary substantially without rational basis between centers and even within centers.

It is unrealistic to expect randomized controlled trials (RCTs) to be performed in the near future in this area. This is because the major pharmaceutical companies are unlikely to engage in the sponsorship of such studies, given the high risk involved in treating convulsive SE, the nature of the drugs involved, and the low frequency of the condition. In addition, the European regulations in their current form for undertaking studies in the emergency situation in patients unable to give consent pose serious obstacles for future research in this area.

SE is defined for the purposes of this document as epileptic activity continuing for 30 minutes or more. The classification of SE used in this document is given in Table 1.

At the workshop, four specific areas were considered.

SPECIFIC EUROPEAN ISSUES CONCERNING REGULATION AND OPTIMIZATION OF THERAPY FOR SE

The workshop suggested that the following measures might be adopted to improve epilepsy care in Europe. These were endorsed by the ILAE Commission on European Affairs (CEA) and it is hoped that these can be considered by other European agencies and professional bodies—including the Task Force in Europe for Drug Development in the Young (TEDDY), ILAE Commission on Pediatrics, European Pediatric Neurology Society, European Federation of Neurological Societies, and societies in other relevant specialties (i.e., intensivists). The regulatory issues
**GRAY MATTERS**

**Table 1. Classification of SE**

<table>
<thead>
<tr>
<th>1. NCSE occurring in the neonatal and infantile epilepsy syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a. Ohtahara syndrome</td>
</tr>
<tr>
<td>1b. West syndrome</td>
</tr>
<tr>
<td>1c. Severe myoclonic encephalopathy of infancy (SMEI; Dravet syndrome)</td>
</tr>
<tr>
<td>1d. NCSE in other forms of neonatal or infantile epilepsy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. NCSE occurring only in childhood</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a. NCSE in early-onset benign childhood occipital epilepsy (Parayiotopoulos syndrome)</td>
</tr>
<tr>
<td>2b. NCSE in other forms of childhood epileptic encephalopathies, syndromes, and etiologies (e.g., Ring chromosome 20, Angelman syndrome, Rett syndrome, myoclonic-astatic epilepsy, other childhood myoclonic encephalopathies)</td>
</tr>
<tr>
<td>2c. Electrical status epilepticus in slow wave sleep (ESES)</td>
</tr>
<tr>
<td>2d. Landau-Kleffner syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Convulsive SE occurring only in childhood</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a. Febrile SE</td>
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</table>

<table>
<thead>
<tr>
<th>4. NCSE occurring in both childhood and adult life with epileptic encephalopathy</th>
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</thead>
<tbody>
<tr>
<td>4a. NCSE in the Lennox-Gastaut syndrome</td>
</tr>
<tr>
<td>4b. Other forms of NCSE in patients with learning disability or disturbed cerebral development (cryptogenic or symptomatic) without epileptic encephalopathy</td>
</tr>
<tr>
<td>4c. Typical absence SE in idiopathic generalized epilepsy</td>
</tr>
<tr>
<td>4d. Complex partial SE:</td>
</tr>
<tr>
<td>i. Limbic</td>
</tr>
<tr>
<td>ii. Nonlimbic</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>4e. NCSE in the postictal phase of tonic–clonic seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>4f. Subtle SE (myoclonic SE occurring in the late stage of convulsive SE)</td>
</tr>
<tr>
<td>4g. Aura continua [with: (i) sensory, (ii) special sensory, (iii) autonomic, (iv) cognitive symptoms]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Convulsive forms of SE occurring in childhood and adult life</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a. Tonic–clonic status epilepticus</td>
</tr>
<tr>
<td>5b. Epilepsia partialis continua (EPC; simple partial motor SE)</td>
</tr>
<tr>
<td>5c. Myoclonic SE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. NCSE occurring in late adult life</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a. De novo absence SE of late onset</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. Boundary syndromes *</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a. Some cases of epileptic encephalopathy</td>
</tr>
<tr>
<td>7b. Some cases of coma due to acute brain injury with epileptiform EEG changes</td>
</tr>
<tr>
<td>7c. Some cases of epileptic behavioral disturbance or psychosis</td>
</tr>
<tr>
<td>7d. Some cases of drug induced or metabolic confusional state with epileptiform EEG changes</td>
</tr>
</tbody>
</table>

*Boundary syndromes are defined as cases in which it is not clear to what extent the continuous epileptiform electrographic abnormalities are contributing to the clinical impairment.*

should be presented by these (and other relevant bodies) to the European regulatory agencies for discussion and action.

**Harmonizing and optimizing care across Europe**

There is a need to document and to harmonize drug availability across Europe, as it is clear that the provision of medicines in different countries varies considerably; this reduces choice and is to the detriment of patients.

The following suggestions for harmonizing and optimizing therapy are made:

1. A list of currently licensed drugs for SE should be prepared (a first draft is at the end of this document—Annex 1. This list demonstrates the variability and inadequacy of current licensing).

2. A list of drugs which are recommended for inclusion in European formularies for SE should be prepared (as a preliminary consideration, the workshop considered this should include: fosphenytoin, lorazepam, midazolam, phenytoin, phenobarbital, and valproate). National authorities should be approached with the approved list to ensure that these are included in national formularies.

3. All countries should have clear guidelines sanctioned by the national ILAE chapter, and other professional bodies, for the optimal treatment of SE.

**Regulatory authorities**

A major issue of concern is that many of the effective drugs for SE are not licensed for this indication. The
question of using the “Orphan Drug” legislation for certain agents has been raised, but SE has been considered too common to be considered an orphan condition. The current European Medicines Agency (EMEA) guideline for the approval of AEDs fails to mention intravenous (IV) formulations, and this is to be revised in 2007. It is also noted that too low an IV dosage of phenytoin is recommended in some regulatory documents.

It was suggested that:

1. The ILAE CEA, TEDDY, European Federation of Neurological Sciences (EFNS), and other bodies should register support for ongoing discussions with the regulatory authorities to facilitate the approval and licensing of appropriate drugs used in the emergency control of seizures (for instance, such drugs as IV or buccal midazolam, IV lorazepam, IV valproate, IV levetiracetam, and IV propofol).

2. The ILAE CEA, which is a contact group of the EMEA, should provide input to the EMEA regarding IV formulations and doses. Other bodies should be encouraged also to provide input.

3. The ILAE CEA should stimulate clinical trails in this area and also encourage EMEA to define design features for clinical trials that would meet regulatory standards. The ILAE CEA should advise regulatory authorities on the relevant and feasible clinical end points that would meet regulatory standards.

Issues of consent

A major issue in clinical trials concerns the recent European regulations concerning protection of subjects who are unable to give consent [this applies for instance to an unconscious patient presenting at an accident and emergency (A&E) with SE]. Recent tightening of European regulations has, on the face of it, made it extremely difficult to conduct clinical trials in SE. There may be national mechanisms for mitigating the rules for appropriate trials, but there is considerable uncertainty in this area.

It was suggested that:

1. ILAE CEA should make representations to clarify and improve the regulations regarding consent for clinical trials in SE. It should contact colleagues in other therapeutic areas with similar difficulties (i.e., stroke or head injury).

Stimulating multicenter collaboration

SE is one area in which multicenter collaboration would be highly appropriate, given the relatively low frequency of some forms and the importance of the condition.

| Table 2. Protocol for the in-hospital treatment of tonic–clonic SE in adults |

<table>
<thead>
<tr>
<th>Stage 1: stage of early status (0–10/30 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Lorazepam: 4 mg IV bolus (can be repeated once)</td>
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<tr>
<td>↓ (if seizures continue after 30 min).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 2: stage of established status (10/30–60/90 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Phenobarbital: IV infusion 10 mg/kg at a max. rate of 100 mg/min, or</td>
</tr>
<tr>
<td>- Phenytoin: IV infusion 15 mg/kg at a max. rate of 50 mg/min, or</td>
</tr>
<tr>
<td>- Fosphenytoin: IV infusion 15 mg PE/kg at 100 mg PE/min, or</td>
</tr>
<tr>
<td>- Valproate: IV infusion 25 mg/kg at 3–6 mg/kg/min</td>
</tr>
<tr>
<td>↓ (if seizures continue after 30–90 min).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 3: stage of refractory status (&gt;60/90 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Propofol: IV bolus 2 mg/kg, repeated if necessary, and then followed by a continuous infusion of 5–10 mg/kg/hour initially, reducing to a dose sufficient to maintain a burst suppression pattern on the EEG (usually 1–3 mg/kg/hour), or</td>
</tr>
<tr>
<td>- Thiopental: IV bolus 100–250 mg given over 20 s with further 50 mg boluses every 2–3 min until seizures are controlled, followed by a continuous IV infusion at a dose sufficient to maintain a burst suppression pattern on the EEG (usually 3–5 mg/kg/hour), or</td>
</tr>
<tr>
<td>- Midazolam: IV bolus 0.1–0.3 mg/kg at a rate not exceeding 4 mg/min initially, followed by a continuous IV infusion at a dose sufficient to maintain a burst suppression pattern on the EEG (usually 0.05–0.4 mg/kg/hour).</td>
</tr>
</tbody>
</table>

When seizures have been controlled for 12 hours, the drug dosage should be slowly reduced over a further 12 hours. If seizures recur, the general anesthetic agent should be given again for another 12 hours, and then withdrawal attempted again. This cycle may need to be repeated every 24 hours until seizure control is achieved.

IV, intravenous; PE, phenytoin equivalents.

It is suggested that the ILAE CEA should support the formation of:

1. A European Registry collecting observational information, recording every off-label use, improving the care standards (based on the similar registries in existence for Fabry’s disease and EURAP).

2. Multicenter clinical trials to identify new improved therapies, particularly in stage 2 and stage 3 of tonic-clonic SE and in less common forms.

TREATMENT OPTIONS FOR GENERALIZED TONIC–CLONIC SE

General framework of a treatment protocol in generalized convulsive SE (GCSE)

There was general agreement on a general framework for the treatment of generalized tonic–clonic SE, although it was recognized that the clinical evidence on which to base drug choice in stages 2 and 3 of the condition is very weak.
Table 3. Complications of tonic–clonic SE

<table>
<thead>
<tr>
<th>Cerebral</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hypoxic/metabolic cerebral damage</td>
<td></td>
</tr>
<tr>
<td>• Excitotoxic (seizure-related) cerebral damage</td>
<td></td>
</tr>
<tr>
<td>• Cerebral edema and raised intracranial pressure</td>
<td></td>
</tr>
<tr>
<td>• Cerebral venous thrombosis</td>
<td></td>
</tr>
<tr>
<td>• Cerebral hemorrhage and infarction</td>
<td></td>
</tr>
<tr>
<td>Cardiorespiratory and autonomic</td>
<td></td>
</tr>
<tr>
<td>• Hypotension</td>
<td></td>
</tr>
<tr>
<td>• Hypertension</td>
<td></td>
</tr>
<tr>
<td>• Cardiac failure</td>
<td></td>
</tr>
<tr>
<td>• Tachy- and brady-arrhythmia, cardiac arrest</td>
<td></td>
</tr>
<tr>
<td>• Respiratory failure</td>
<td></td>
</tr>
<tr>
<td>• Disturbances of respiratory rate, rhythm, and apnea</td>
<td></td>
</tr>
<tr>
<td>• Pulmonary edema, hypertension, embolism, pneumonia, aspiration</td>
<td></td>
</tr>
<tr>
<td>• Hyperpyrexia</td>
<td></td>
</tr>
<tr>
<td>• Sweating, hypersecretion, tracheobronchial obstruction</td>
<td></td>
</tr>
<tr>
<td>• Peripheral ischemia</td>
<td></td>
</tr>
<tr>
<td>• Metabolic and systemic</td>
<td></td>
</tr>
<tr>
<td>• Dehydration</td>
<td></td>
</tr>
<tr>
<td>• Electrolyte disturbance (especially hypoglycemia, hyponatremia, hypokalemia)</td>
<td></td>
</tr>
<tr>
<td>• Acute renal failure (especially acute tubular necrosis)</td>
<td></td>
</tr>
<tr>
<td>• Acute hepatic failure</td>
<td></td>
</tr>
<tr>
<td>• Acute pancreatitis</td>
<td></td>
</tr>
<tr>
<td>• Disseminated intravascular coagulopathy/multiorgan failure</td>
<td></td>
</tr>
<tr>
<td>• Rhabdomyolysis</td>
<td></td>
</tr>
<tr>
<td>• Fractures</td>
<td></td>
</tr>
<tr>
<td>• Infections (pulmonary, skin, urinary, septicemia)</td>
<td></td>
</tr>
<tr>
<td>• Thrombophlebitis, dermal injury</td>
<td></td>
</tr>
</tbody>
</table>

The following recommendations for a general treatment protocol are made:

1. All units should have a written protocol for the therapy of convulsive SE. These should be agreed with colleagues in other disciplines and may be hospital-specific. Cardiorespiratory function should be continuously monitored if IV therapy is being given.

2. The protocol should be staged with a clear structured time frame (Table 2 gives an example of a widely used staged protocol).

3. General emergency management is essential. Support of cardiovascular function, which is often compromised, is vital, as well as the identification and treatment of other complications (Table 3).

4. Investigations to determine the cause of SE must be carried out without delay of initial treatment.

5. Intravenous (IV) therapy is preferred where facilities for resuscitation are available, but should not generally be started in situations where facilities for resuscitation do not exist (i.e., out-of-hospital). In these situations, emergency therapy using alternative routes of administration should be used (i.e., intranasal midazolam, buccal midazolam, or rectal diazepam).

6. There is good RCT evidence in early status (stage 1) that the early and rapidly instituted use of benzodiazepines (in sufficient dose) is the preferred treatment (Table 4). There is at least one RCT and metaanalysis that conclude that lorazepam is slightly superior to diazepam. Treatment with benzodiazepine can be repeated on a second occasion after 5–10 min if necessary.

7. If benzodiazepine treatment fails to control seizures, the patient should be considered to be in the stage of established SE (stage 2), and this requires the rapid institution of IV antiepileptic drugs. Phenytoin or phenobarbital are commonly used, although alternative drugs exist (Table 5).

8. If treatment in the stage of established SE fails to control seizures, the patient should be considered to enter the stage of refractory SE (stage 3), and general anesthesia should be instituted as soon as possible (Table 6). It is not appropriate to cycle through alternative treatments in the stage of established status and delay anesthetic treatment unless there are unavoidable resource difficulties. The anesthesia not infrequently needs to be continued for days or weeks. EEG monitoring is essential during anesthesia for refractory SE.

9. At all stages, the patients who have been administered parenteral medication must be continuously observed by a competent person to monitor cardiorespiratory function.

Table 4. Drugs used in the stage of early tonic–clonic SE (Stage 1)

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Adult dose</th>
<th>Pediatric dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>IV bolus (not exceeding 2–5 mg/min)</td>
<td>10–20 mg</td>
</tr>
<tr>
<td></td>
<td>Rectal administration</td>
<td>10–30 mg</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>IV bolus (not exceeding 2 mg/min)</td>
<td>1–2 mg at 2 mg/min*</td>
</tr>
<tr>
<td></td>
<td>Buccal or intranasal</td>
<td>0.07 mg/kg (usually 4 mg)*</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>IV bolus</td>
<td>0.07 mg/kg (usually 4 mg)*</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Buccal or intranasal</td>
<td>5–10 mg*</td>
</tr>
</tbody>
</table>

*May be repeated; PE, phenytoin equivalents; IV, intravenous; IM, intramuscular.
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<table>
<thead>
<tr>
<th>Table 5. Drugs used in the stage of established tonic–clonic SE (Stage 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route of administration</strong></td>
</tr>
<tr>
<td>Fosphenytoin</td>
</tr>
<tr>
<td>Levetiracetam</td>
</tr>
<tr>
<td>Phenytoin</td>
</tr>
<tr>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Valproate</td>
</tr>
</tbody>
</table>

PE, phenytoin equivalents; IV, intravenous; n/a, not applicable.

10. In SE, due to drug withdrawal/reduction (in patients with preexisting epilepsy) the withdrawn drug should be reintroduced immediately by the intravenous route if possible, and this will usually in itself result in the resolution of the SE.

11. In cases of SE in the postoperative neurosurgical setting, early intubation and anesthesia should be considered in view of the special risks.

It was recognized that treatment failures are often the result of:
1. Underdosing at the stage of established SE.
2. Neglecting maintenance therapy. Emergency therapy with lorazepam, phenytoin, or phenobarbital will have an effect for up to 12 hours, and if maintenance antiepileptic therapy has not been adequately introduced within this period, relapse of the SE is common.
3. Misdiagnosis, and particularly confusion with psychogenic nonepileptic status or drug-induced or metabolic encephalopathy.
4. Failure to identify and treat the underlying etiology of the SE or the secondary complications (Table 3).

It was also recognized that a number of factors influence the choice of AED used in status. These factors include: comorbidity, age, and epilepsy syndrome.

**Treatment options for the stage of early SE (stage 1)**

There is general agreement that initial treatment should be with benzodiazepines. This should be given via the IV route wherever possible (usually in hospital settings), but out-of-hospital treatments with alternative modes of administration are better than delaying therapy.

**Table 6. Anesthetic drugs used in adults in the stage of refractory tonic–clonic SE (stage 3)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>0.1–0.3 mg/kg at 4 mg/min bolus followed by infusion of 0.05–0.4 mg/kg/hour</td>
</tr>
<tr>
<td>Thiopentone</td>
<td>100–250 mg bolus over 20 s then further 50 mg boluses every 2–3 min until seizures are controlled. Then an infusion of 3–5 mg/kg/hour to maintain burst suppression</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>10–20 mg/kg bolus at 25 mg/min followed by an infusion of 0.5–1 mg/kg/hour increasing to 1–3 mg/kg/hour to maintain burst suppression</td>
</tr>
<tr>
<td>Propofol</td>
<td>2 mg/kg bolus followed by an infusion of 5–10 mg/kg/hour to maintain burst suppression</td>
</tr>
</tbody>
</table>

The options for AED therapy include:
1. Out-of-hospital treatment: Non-IV therapy is recommended where facilities for resuscitation do not exist. The usual chosen options are the use of rectal diazepam, buccal midazolam, or intranasal midazolam. There is one well-conducted RCT that favors buccal midazolam over rectal diazepam. In out-of-hospital situations where facilities for resuscitation and cardiorespiratory monitoring exists, IV treatment can be started (see no.2).
2. In-hospital treatment (and in other special settings where facilities for resuscitation exist): Use of IV therapy is recommended. Diazepam, lorazepam, and clonazepam can be used, and several trials have favored lorazepam.

**Treatment options for the stage of established SE (stage 2)**

Therapy in this stage has been traditionally with IV phenytoin or IV phenobarbital, although there is considerable recent uncontrolled evidence suggesting that IV valproate is a good alternative to these traditional therapies. There is also promising uncontrolled evidence suggesting that IV levetiracetam may be a good alternative mode of therapy.

The options for AED therapy include:
1. The use of either: phenytoin, fosphenytoin, phenobarbital, valproate, or levetiracetam. There are several RCTs showing that phenytoin and phenobarbital have equivalent efficacy. There is an RCT showing that fosphenytoin has superior tolerability compared to phenytoin in the setting of acute seizures (but not SE).
Treatment options for the stage of refractory status (stage 3)

Treatment with general anesthesia requires the full panoply of intensive therapy unit (ITU) facilities and ideally also continuous or at least intermittent/repeated electroencephalography (EEG) monitoring.

The options for anesthetic drug treatment include:
1. Midazolam, propofol, or thiopental (pentobarbital) are the most commonly used, although there are no RCT comparing outcome. Other anesthetic options, less commonly used, include ketamine and the inhalational anesthetics.
2. Hypothermia may improve outcome. It should be considered in ITU settings if available.

THE TREATMENT OF NONCONVULSIVE SE

The treatment options depend on the type of nonconvulsive SE (NCSE).

Absence SE (in idiopathic generalized epilepsy)
This requires urgent therapy and can be started out of hospital.

The options for treatment include:
1. An oral benzodiazepine, such as lorazepam, clobazam, diazepam, or midazolam is first-line therapy and should be given as soon as possible (out-of-hospital if necessary).
2. If this does not resolve the condition, IV therapy should be given, but this requires hospitalization and preferably EEG monitoring. The usual initial IV therapy is with low dose diazepam or lorazepam.
3. In the cases in which IV benzodiazepines are not effective, there is open trial evidence that suggests that IV valproate or levetiracetam can be effective.

Complex partial SE
Out-of-hospital treatment is not recommended except in exceptional circumstances—for instance in patients with partial epilepsy and EEG confirmed prior episodes presenting with identical symptoms. In this situation, out-of-hospital treatment with oral, buccal, nasal, or rectal benzodiazepine treatment can be given. Where there is diagnostic uncertainty and/or management concerns, admission is required.

The following treatment suggestions are made:
1. Urgent EEG is recommended wherever possible. A review by an experienced neurologist is important to avoid diagnostic error.

2. In patients with epilepsy in whom complex partial SE is strongly suspected and in whom no other cause is identified, oral or IV antiepileptic drugs should be given (the route of administration depends on the severity of the condition). Options include: IV valproate, benzodiazepine (preferably lorazepam 4 mg), or phenytoin/fosphenytoin. Wherever possible, this should be carried out with EEG monitoring.
3. EEG is diagnostic and should be arranged as soon as possible.
4. The choice of therapy will depend on age, comorbidity, level of consciousness, and etiology. This will also influence the intensity of treatment, and anesthesia (with intubation, ITU facilities, and continuous EEG monitoring) is needed in cases in which there is a severe life-threatening etiology.

De novo absence SE of late onset
This condition is often the result of psychotropic drug withdrawal or is a late recurrence of idiopathic generalized epilepsy.

The options for treatment include:
1. Low dose IV benzodiazepine (i.e., lorazepam 1 mg) should be given, with EEG monitoring. IV therapy should only be given where resuscitation facilities are available. There may not be an immediate clinical response, and the dose can be repeated. In almost all cases, the SE can be controlled in this way.
2. Long-term antiepileptic therapy is indicated if there are focal abnormalities on magnetic resonance imaging (MRI) or EEG, or if there are no identifiable provoking factors.

ISSUES SPECIFIC TO PEDIATRIC SE

Convulsive SE (tonic–clonic SE) in children
This was considered separately during the workshop, and the following conclusions were arrived at:

Stage of early status (stage 1)
There is an almost universal consensus that a benzodiazepine should be used as a drug of choice in treatment of a prolonged seizure or in early SE in children (including febrile SE); the therapy follows similar lines to that in adults. Which benzodiazepine is likely to be country-dependent, but it is recommended that guidelines should be available in each country as to which one and what dose, and by which route it should be administered. It is important that prehospital treatment should be part of the guideline.
GRAY MATTERS

There remains a likely gap however between recommendations and actual emergency treatment administered. This requires education, including what defines a prolonged seizure, what may be seen as continuing seizure activity, and also when to treat acute repetitive seizures. There is also a need for education regarding the recognition of acute symptomatic seizures and psychogenic seizures.

It is suggested that:
1. Treatment protocols for children should be available in all countries.
2. A target is set of 80% of individuals to be treated appropriately. Educational initiatives should be put in place for diagnosis and treatment.

Stage of established SE (stage 2)
Evidence on the relative advantages and disadvantages of different therapies in children is deficient. It is unlikely that pediatricians could be persuaded to use IV valproate in the de novo acute situation in view of the risk of unrecognized metabolic disease. In addition, there is enough evidence of extravasation injury with phenytoin use to feel fosphenytoin should be compared against phenobarbitone or levetiracetam. There is no evidence that any agent is more superior in efficacy over another—what is used in individual countries will depend on availability and tradition. There is a need formally to assess efficacy and safety.

It is suggested that:
1. An RCT is conducted, comparing what is optimal medication in children as in adults in established SE.

Stage of refractory SE (stage 3)
As in adults, there is a clear need for protocol and audit with regard to when to proceed to anesthesia and which anesthetic to use. This will again depend on experience and tradition. There is also a need for statement with regard to EEG monitoring.

It is suggested that:
1. A protocol is prepared regarding the choice of anesthetic and EEG monitoring.

Specific childhood forms of NCSE
The treatment depends on the type (see Table 1). NCSE in epileptic encephalopathies needs to be assessed in a syndrome-specific way. NCSE cannot be compared across syndromes. The outcome expected differs. The aim of therapy in Panayiotopoulos syndrome, Rett syndrome, electrical SE in slow wave sleep (ESES), Lennox-Gastaut syndrome, and Landau-Kleffner syndrome are quite different. There are no randomized trials in any of these forms of NCSE comparing treatment options. Universal guidance cannot therefore be given.

It is suggested that:
1. A “registry” should be compiled with single sheet data with regard to clinical presentation, behavioral questionnaire, EEG criteria, details of treatment, and follow-up data. This data could be collected and analyzed prior to next SE workshop, from which study or treatment recommendations could be discussed.

OTHER FORMS OF SE
Epilepsia partialis continua (EPC)
It was recognized that treatment is very dependent on (1) the etiology of the condition—this is fundamental, and where possible, treatment should be aimed at alleviating the etiology as a way of resolving the epilepsy; (2) the severity of the condition; (3) acute EPC requires a different approach to chronic EPC. In view of these variables, it has not been possible to devise simple guidelines for the treatment of EPC, which cover all clinical eventualities. Nevertheless, there is a fair degree of consensus on the various treatment options available.

The options for management include the following points:
1. In the acute phase, AEDs may be helpful, and any drug effective in chronic epilepsy may be tried. Even if the focal jerking can not be completely prevented, the antiepileptics have a vital role in preventing secondary generalization. There are no large series that can provide reliable information as to which drugs are required.
2. In the chronic phase, the jerking may not respond to AED therapy even in high doses, but again antiepileptics have a role in minimizing symptoms and preventing secondary generalization.
3. Steroids are sometimes given, but their effectiveness is not established, and their role is probably more in suppressing inflammatory etiologies rather than through a specifically antiepileptic action.
4. Intravenous immunoglobulin (IVIG) and plasma exchange are now also recommended, and can be profoundly effective, but again their role is probably more in suppressing inflammatory etiologies rather than through a specifically antiepileptic action.
5. Surgical therapy, including resective surgery, thalamic stimulation, and also transcranial magnetic stimulation (TMS), has been recommended in individual cases. Again, opinion differs as to its role.
It is also suggested that:
1. As the condition is rare and heterogeneous, an RCT is not feasible. In this situation, it is recommended that a European registry is developed with active surveillance in order to develop observational data on treatment outcome.

Myoclonic SE in coma
This form of SE usually occurs in the context of severe brain injury as a result of anoxia (for instance after delayed resuscitation following cardiac arrest). The EEG may show periodic lateralized epileptiform discharges (PLEDs) or generalized periodic spiking (GPS), and the management of this is controversial. There are no well conducted randomized studies, and guidance is difficult to give.

Options for management include:
1. Anticonvulsant therapy with IV barbiturate, propofol, or other anesthetics to abolish the PLED pattern on the EEG.
2. Cooling—this has been shown to improve outcome.
3. AED therapy to control EEG changes suggesting evolving seizures.

It is also recommended that:
1. EEG monitoring is optimal in this situation, but in many centers this is not available. Intermittent EEG monitoring is a good alternative, but the use of a cerebral function monitor is not recommended. EEGs can be read online off-site if there are no available neurophysiologists.
2. There is a tendency for anesthetic decisions not to account for neurological factors, to the detriment of patients and neurologists. Therefore, neurologists, as well as intensivists should be involved in the management of this and other forms of SE.

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Conflict of interest: We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors has any conflicts of interest to disclose.

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Annex 1. Availability and licensing of drugs for SE in European countries.

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Reg.f.SE, registered for use in SE.

*Valproate intravenous (IV) is licensed but not marketed.

Transatlantic similarities and differences in the management of status epilepticus

In April 2007, a group of epileptologists with major interests in status epilepticus (SE) met under the auspices of the National Hospital for Neurology and Neurosurgery in London (Queen Square) to discuss the state of our knowledge of this devastating problem. One of the workshops held at this conference concentrated on developing consensus and identifying problems for study that could form an appropriate report to the Commission on European Affairs of the International League Against Epilepsy (ILAE) (Shorvon et al., 2008). I had the privilege of attending the workshop. As I listened to the participants, I was struck by the major similarities and the few, but potentially important differences, in the management of SE on opposite sides of the Pond.

In Europe, there is more emphasis on licensure for a particular indication (such as SE) than in North America. Once a drug is initially approved for clinical use, the major reason that a sponsor west of the Atlantic seeks a new indication is to advertise it. Many drugs used to terminate SE, and most employed for refractory SE, do not have an officially sanctioned indication for this purpose. While there are rare circumstances in which the lack of such an indication hampers the physician’s ability to use a drug, most physicians in North America ignore the issue. The European consensus report indicates that such implicit approval would be useful also in Europe.

A more pressing problem is that some of the commonly used parenteral anticonvulsants are not available in some European countries. The report stresses the advantages of having guidelines for the use of these drugs, guidelines that would be promulgated by the national chapters of the ILAE. Several European countries have already set forth recommended guidelines. In this regard, they are far ahead of their North American colleagues. The Epilepsy Foundation of America has assembled a group to develop guidelines for the management of refractory SE, but these guidelines have yet to be completed.

In the early treatment of SE, there is essentially complete agreement between Europe and North America, except for the dose of lorazepam suggested. Based on the results of the VA cooperative trial, the usual dose in North
America is 0.1 mg/kg (Treiman et al., 1998), whereas the European consensus report suggests a 4 mg dose, which may be repeated once. There are no trials comparing these two approaches directly. The reported response rate to the single 0.1 mg/kg dose was 65%, while in the San Francisco prehospital study 59% of patients responded to either 2 or 4 mg of lorazepam (Alldredge et al., 2001). These studies are not strictly comparable on many levels, most importantly because the patients in the San Francisco study were treated much earlier in their course of SE than patients in the VA cooperative trial. Tachyphylaxis to the anticonvulsant effect of benzodiazepines develops very rapidly (Goodkin et al., 2007). Thus, if the European regimen is employed, the risk of drug failure may increase over that expected with the 0.1 mg/kg dose. Parenthetically, as the populations of both North America and Europe become more obese, the appropriate doses of fatsoluble agents such as the benzodiazepines may need reconsideration.

The designation of a time frame for designating a state of “established SE,” beginning between 10 and 30 minutes after seizure onset, is in concert with the San Francisco prehospital experience, and some of us have argued that a similar standard be accepted more widely (Lowenstein et al., 1999). However, this change in definition has not been generally accepted, even as an increasing number of practitioners advocate for the earlier treatment (e.g. after five to ten minutes) of patients whose seizures do not stop spontaneously, in order to prevent their transition into increasing degrees of pharmacologic resistance (Shinnar et al., 2001). The European consensus document suggests that a second, nonbenzodiazepine agent be used at this point; it recommends a hydantoin, phenobarbital, or valproate. Each of these drugs has efficacy as a first-line agent, but evidence for their efficacy as a subsequent therapy is lacking (vide infra). These drugs are also very commonly recommended as second-line agents in North America.

Similarly, the European consensus report implies a temporal component to the designation of refractory SE, suggesting that refractoriness occurs between 60 and 90 minutes. There is not even a hint of an agreement on the definition of refractory SE in North America; to the extent that authors have used operational definitions, they have concentrated on the numbers and classes of drugs that have failed rather than on a particular duration. Data from the VA cooperative trial suggest that the likelihood that a second conventional agent will succeed after the first drug has failed is about 7%, suggesting (at least to me) that the patient should be considered refractory when the first administered anticonvulsant fails (Bleck, 2006). At this point, there are precious few data upon which to base a therapeutic decision, and the recommendations for propofol, thiopental, or high-dose midazolam all have modest support in the literature.

The discussion of causes for treatment failure is an area frequently overlooked in publications about SE. The authors touch upon failure to provide maintenance anticonvulsants, to treat the etiology of the condition as well as its manifestations, and confusion with other, nonepileptic conditions that may be confused with SE.

The document also considers therapy for nonconvulsive forms of SE – an area in which there has been little research with sufficiently large populations to make firm recommendations. The discussion here is based on personal experience and common sense; I see no differences between the continents in the approach to these conditions. This is true, as well, of the sections discussing childhood (pediatric) SE, epilepsy partialis continua, and myoclonic SE following anoxic event. The authors properly stress the importance of cooling after cardiac arrest, a therapy which our European colleagues have been much faster to embrace than their American cousins.

In sum, there is much more to celebrate in our similarities than to complain about in our differences. However, those differences hold the germs of some important research questions that should be investigated throughout the world.

Conflict of interest: I confirm that I have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The author has no conflict of interest to declare.

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### Status epilepticus—An Australian perspective

Australia is a large and sparsely populated country, with the great majority of the population living in a few large coastal cities. Outside of the large cities, a few of the larger regional centers have neurologists and EEG services. However, most rural and remote hospitals do not. In some communities, nurses provide primary health care. Treatment of status epilepticus (SE) in small rural hospitals is carried out by general practitioners, sometimes in telephone consultation with neurologists, pediatric neurologists, or intensivists. Transport to a center where there is a neurologist and EEG service may involve distances of thousands of kilometers and transport by air ambulance. Retrieval services, such as the Royal Flying Doctor Service, are usually staffed by intensive care specialists and often supervise the initial treatment of SE, including intubation, before transfer. Neurologists and pediatric neurologists are more likely to be consulted if the patient is already known to have epilepsy.

SE may have different features in indigenous Australians. A total of 53% of adult patients admitted with SE to Cairns Base Hospital in Far North Queensland were indigenous, whereas indigenous people made up only 13% of the catchment population and 20% of all hospital admissions (Archer & Bunby, 2006). Alcohol use did not appear to explain this difference. This high rate of SE coupled with very long distances to adequate facilities for treatment pose particularly difficult challenges.

The last two decades have seen the development of emergency medicine as a recognized medical specialty in Australia. These physicians generally institute therapy for SE before consulting the neurology service. This means that neurologists are not involved in the initial management. This has the advantage of reducing delay in initiating treatment but the disadvantage that involvement by neurologists is delayed. Often, by the time the neurology team is consulted, the patient is already intubated, ventilated, and sedated, so that the neurologist has no opportunity to witness seizures or adequately examine the patient. The neurologist has to make the diagnosis in retrospect, with the risk that pseudo-SE may not be recognized, the nature of the seizures may be unclear and the neurological examination will be limited. There is a tendency to treat patients more aggressively than necessary, with a low threshold for intubation, ventilation, and sedation.

Patients with epilepsy living in remote areas may benefit from buccal or intranasal benzodiazepines and their families, especially when the patient is a child, are usually instructed in their use. However, failure to appreciate the distinction in risk between acute repetitive or prolonged seizures and SE encourages their unnecessary use in urban patients without an increased risk of SE, in whom they may be prescribed indiscriminately. This practice was reinforced by a lawsuit in which a pediatric neurologist was sued for failing to prescribe rectal diazepam for a child with well-controlled epilepsy, who suffered brain damage following an episode of SE (Lowens v Woods, 1996). The trial judge found the neurologist negligent but the judgement was overturned on appeal. Guidelines were subsequently published in an attempt to temper enthusiasm for out-of-hospital benzodiazepine use (Somerville & Antony, 1995).

Most of the shortcomings of the current treatment of SE listed in the preceding workshop report by Shorvon and colleagues apply also in Australia.

Awareness of nonconvulsive SE remains low, particularly among nonneurologists. This is compounded by limited availability of urgent EEG outside of teaching hospitals. The lack of availability of non-sedating intravenous antiepileptic drugs (AEDs) other than phenytoin and the reluctance of some intensive care units to admit nonventilated patients makes the choice of treatment of nonconvulsive status epilepticus (NCSE) difficult when phenytoin has failed. The recent arrival of intravenous levetiracetam is therefore welcome.

Phenytoin loading doses are often inadequate, usually consisting of a standard 1 g dose irrespective of body weight. Serum levels are rarely performed to confirm adequacy of the loading dose and when they are, further loading doses are also frequently inadequate.

Of the IV benzodiazepines, only diazepam and clonazepam are registered for the treatment of seizures. However, IV midazolam is widely used, resulting in the ironic situation where a state government health department has issued a policy directive for the treatment of seizures in children that recommends the use of an unregistered drug (Department of Health New South Wales, 2006). Lorazepam is available only in tablet form. Fosphenytoin was registered in 2000 but soon withdrawn because of poor sales volume. Although intravenous valproate was registered in Australia in 2005, because of limited supplies worldwide, it will not be available until late 2008 at the earliest.

Urgent EEG is largely restricted to teaching hospitals. Few centers possess equipment for continuous EEG monitoring in the intensive care unit, although single or dual channel monitors or BIS (bispectral index) systems are sometimes used.
Conflict of interest: We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Neither of the authors has any conflicts of interest to disclose.

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GRAY MATTERS

To the Editors:

I read with great interest the recent supplement (November 2007), in which presentations from the First London Colloquium on Status Epilepticus were published. It is encouraging to learn of the progress that is being made in the understanding and management of this serious disorder. However, I think that Drs. Shorvon, Trinka, and Walker are being unduly pessimistic when they state that “the reluctance of the pharmaceutical industry to engage in a clinical trial . . . , as well as the EC regulations for clinical trials in noncompetent persons, make it unrealistic to hope that randomized controlled trials will answer our questions in the near future.” (Shorvon et al., 2007) Large multicenter studies comparing different antiepileptic drugs could be performed in patients with status epilepticus by using the Internet to recruit patients. The treating doctor could log on to a Website, and answer a small number of questions regarding the patient and the status (e.g., what type of status epilepticus does this patient have? Is the cause known? Is the patient taking any antiepileptic drugs? What other drugs is the patient taking? Are any of the study drugs contraindicated? Has the patient had an EEG?) For each question, there would be a list of options from which the doctor would select the appropriate response. If the patient fulfilled predetermined criteria, the patient would be randomized online, and instructions would be given for treatment with the appropriate drug. It would be possible to fill in the online form and receive a response within 2 or 3 min. Follow-up data would be collected online at varying intervals. If the patient did not fulfill the specific criteria, the doctor could be directed to published guidelines. Patients could be selected for different studies depending on the etiology. Studies of refractory patients in intensive care units could be performed in a similar manner.

We recently described how the Internet could be used to recruit patients with epilepsy for randomized controlled trials of antiepileptic drugs (Bergin et al., 2007). This approach could be adapted relatively easily to perform randomized controlled trials of drugs in status epilepticus.

I do not know the specific details regarding studies in noncompetent persons in Europe, and some ethics committees may not approve these studies. However, I would hope that many ethical committees would agree that such studies are acceptable, if there is genuine uncertainty regarding the optimal treatment, and the study has a high likelihood of resolving this issue. Moreover, I would argue that the medical profession has an ethical duty to try to determine what the best treatment is in these circumstances. I do not think we should simply accept that we cannot perform randomized controlled trials in status epilepticus. I believe the logistics of setting up Internet-based randomized controlled trials would be relatively straightforward, and I would hope that the ethical issues could be overcome in enough centers that studies comparing different drugs in specific forms of status epilepticus could be performed. I encourage the Epilepsy community to explore the potential of this approach.

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REFERENCES


To the Editors:

There is increasing data to support the efficacy and safety of levetiracetam (LEV) in the treatment of idiopathic generalized epilepsies (IGE) (Gründewald, 2005; Berkovic et al., 2007). However, the successful use of oral or intravenous (i.v.) LEV in patients with IGE presenting with absence status epilepticus (ASE) has not been reported to date.

In a 37-year-old male, history and video-EEG disclosed IGE with the first manifestation of a generalized tonic-clonic seizure at the age of 27 years and frequent ASE with cognitive impairment of mild to moderate severity lasting up to several days. Previous antiepileptic medication included valproic acid, lamotrigine, topiramate, and zonisamide, but not LEV. After withdrawal of antiepileptic drugs during video-EEG monitoring, a habitual ASE occurred which was characterized by subtle but consistent attentional and executive disturbances as well as a cognitive slowing of fluctuating albeit gradually augmenting intensity. The patient was still responsive and showed good recollection of ictal events. The EEG displayed discontinuous generalized 3–5 Hz sharp-slow-wave-complexes. The number and the duration of these epileptiform potentials substantially increased in the course of the ASE.

About 19 h after the clinical onset of ASE, neuropsychological examination by the Trail Making Test A and B (Reitan, 1992) revealed a marked reduction of cognitive speed and mental flexibility. Generalized epileptic activity was present in up to 60% of the time on surface EEG. The patient eventually stated that the subjective strain was no longer tolerable.

We therefore administered 500 mg i.v. LEV within 5 min. After 20 min, additional 500 mg LEV was infused over 15 min. After the administration of the first 250 mg i.v. LEV, the patient reported a substantial relief; and after infusion of 500 mg LEV, he felt that he was back to his normal self. Repeated neuropsychological examination after i.v. administration of 500 and 1,000 mg LEV
revealed a dose-dependent improvement in cognitive performance, which finally reached a normal level after application of 1,000 mg i.v. LEV (Fig. 1A and 1B). Accordingly, a dose-dependent reduction down to baseline values of both the number of the generalized epileptiform potentials and the total of their duration was observed (Fig. 1C and 1D). The clinical and electrophysiological effects of i.v. LEV were sustained without any relapse during the following 6 h of observation. There were no adverse reactions.

ASE is a prolonged nonconvulsive state of ongoing or intermittent epileptic activity with cognitive or behavioral changes. Established therapeutic options include the i.v. administration of a benzodiazepine or valproic acid (Kaplan, 2005; Shorvon & Walker, 2005). However, sedation or respiratory depression is not uncommon after administration of benzodiazepines.

In our patient with IGE, low-dose i.v. LEV led to an immediate and sustained interruption of a prolonged ASE without any undesired side effects.

As reported in complex focal status epilepticus in focal epilepsies (Knake et al., 2008; Schulze-Bonhage et al., 2007), also in IGE the administration of i.v. LEV may be an effective and well-tolerated alternative to benzodiazepines in the treatment of nonconvulsive status epilepticus.

Conflict of interest: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors has any conflict of interest to disclose.

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REFERENCES


NEXT MONTH IN Epilepsia

The August issue of Epilepsia presents a series of papers covering various aspects of temporal lobe epilepsy, with a particular emphasis on surgical approaches. The issue is introduced by a critical review of “the quest for optimal extent of resection” by Dr. Schramm, and is followed by full-length research articles on outcome predictors and prognosis, language lateralization, verbal and visual memory, and other TLE-surgery topics. The TLE theme is echoed in several imaging investigations, including a novel study of functionalized magnetonanoparticles for MRI diagnosis and localization. The August issue also includes reports on topics such as first unprovoked seizures, seizure remission and relapse, and seizures associated with work-related stress. Finally, the 9th Workshop on the Neurobiology of Epilepsy (WONOEP) – dealing with “transition from the interictal to the ictal state” – is summarized in Gray Matters.

ONLINE EARLY

Binder et al., “Use of preoperative functional MRI to predict verbal memory decline after temporal lobe epilepsy surgery”

Caraballo et al., “Epileptic encephalopathy with continuous spikes and waves during sleep in children with shunted hydrocephalus: A study of nine cases”

Cavus et al., “Decreased hippocampal volume on MRI is associated with increased extracellular glutamate in epilepsy patients”

Choi et al., “Seizure remission and relapse in adults with intractable epilepsy: A cohort study”

El-Khayat et al., “Reproductive hormonal changes and catamenial pattern in adolescent females with epilepsy”

Figueiredo et al., “Adaptive visual memory reorganization in right medial temporal lobe epilepsy”

Götz-Trabert, et al., “Spread of ictal activity in focal epilepsy”

Gwinn et al., “Local spatial effect of 50 Hz cortical stimulation in humans”

Helbig et al., “Gene expression analysis in absence epilepsy using a monozygotic twin design”

Kavros et al., “Attention impairment in rolandic epilepsy: Systematic review”

Kossoff et al., “A case-control evaluation of the ketogenic diet versus ACTH for new-onset infantile spasms”

Manni et al., “The FLEP scale in diagnosing nocturnal frontal lobe epilepsy, NREM and REM parasomnias: Data from a tertiary sleep and epilepsy unit”
Moeller et al., “Simultaneous EEG-fMRI in drug-naïve children with newly diagnosed absence epilepsy”

Munakata & Tsuchiya, “Residual effect of a 7-amino metabolite of clonazepam on GABA_A receptor function in the nucleus reticularis thalami of the rat”

Rodrigo et al., “Language lateralization in temporal lobe epilepsy using functional MRI and probabilistic tractography”

Schramm, “Temporal lobe epilepsy surgery and the quest for optimal extent of resection: A review”

Selkirk et al., “Clinical differences between patients with nonepileptic seizures who report antecedent sexual abuse and those who do not”

Yamasaki et al., “Neural basis of photo/chromatic sensitivity in adolescence”

ANNOUNCEMENTS

Advanced International Course: Bridging Basic with Clinical Epileptology

The International School of Neurological Sciences in Venice (ISNV) presents a Summer School Course on Bridging Basic with Clinical Epileptology, on July 28–August 8, 2008, at Venice International University, San Servolo, Venice, Italy. Sponsored by the European Community EPILEARN program, ILAE, EUREPA, and Fondazione Istituto Neurologico Carlo Besta, the Course is designed for PhD students and postdoctoral fellows, to help attendees acquire basic and clinical understanding of the epilepsies, and to critically evaluate the literature and prepare grant applications. Course directors are Marco de Curtis (Italy) and Uwe Heinemann (Germany). Further information is available at http://www.epilepsy-academy.org.

AES Epilepsy Research Recognition Award

The AES is pleased to announce the call for applications and nominations for the annual Epilepsy Research Recognition Awards Program. This public recognition program is designed to encourage and reward clinical and basic science investigators whose research contributes importantly to understanding and conquering epilepsy. Deadline for nominations is August 1, 2008. For more information, go to http://www.aesnet.org/go/research/research-awards/epilepsy-research-awards-program.

AES Grants for Innovative, Collaborative Research

The American Epilepsy Society has established a novel grant opportunity that will provide seed support to encourage innovative, collaborative basic or clinical research. Awards from the Research Initiative Fund will be given to AES members who are established investigators. Investigators are encouraged to think “outside the box” and to involve other established investigators who may not be working in the epilepsy field. Letters of Intent are due August 25, 2008. For more information go to http://www.aesnet.org/go/research/research-awards/research-initiative-awards.

Research Infrastructure Awards Program

The AES and the Epilepsy Foundation are partnering to provide an opportunity for scientists to obtain support for nationwide or international networks of clinical or basic science researchers focused on understanding the causes, consequences and treatment of epilepsy. Multi-center research programs are viewed as important mechanisms through which investigators from around the world can establish centralized databases, common protocols, shared resources, core laboratories and exchange rapidly developing techniques and technologies. The funds are to be used to support pilot projects, and/or to hold organizational and planning sessions. Awards will be given for up to $50,000 per year for two years. Letters of intent are due August 25, 2008. For more information, go to http://www.aesnet.org/go/research/research-awards/research-infrastructure-awards.

Early Career Physician-Scientist Award

The Milken Family Foundation and the American Epilepsy Society announce the call for applications for the Early Career Physician-Scientists awards, open to investigators from around the world. This award is designed to assist physician-scientists embarking on early academic careers devoted to epilepsy research. Preference is given to innovative studies leading to new treatments or other novel translational research. $50,000 USD is awarded for a 12 month period beginning in January 2009. Applications are due by Monday, September 8, 2008. Eligibility requirements and application information are available at http://www.aesnet.org/go/research/aes-sponsored-grant-program.
GRAY MATTERS

2nd Baltic Sea Summer School on Epilepsy

The 2nd Baltic Sea Summer School on Epilepsy will take place from August 31–September 4, 2008, close to Copenhagen, Denmark. Please see the EUREPA website http://www.epilepsy-academy.org for further information, or contact Petra Novotny at petra@epilepsy-academy.org.

8th European Congress on Epileptology

The 8th European Congress on Epileptology will take place in Berlin, Germany, September 21–25, 2008. It is presented under the auspices of the German and Israeli ILAE chapters. For more information go to: http://www.epilepsyberlin2008.org/.

VIREPA Distance Learning Courses 2008/2009

Four VIREPA e-moderated distance learning courses will start again in October 2008. The courses are: “Genetics of Epilepsy,” “EEG in the diagnosis and management of epilepsy,” “Neuroimaging” and “Clinical Pharmacology and Pharmacotherapy.” An introductory meeting for participants of all courses (not mandatory) will take place during the 8th European Congress on Epileptology in Berlin in September 2008. The deadline for application to all courses is August 1, 2008. For detailed information and application, please see http://www.epilepsy-academy.org or contact the Epilepsy Academy Office at office@epilepsy-academy.org.

11th European Conference on Epilepsy & Society

The 11th European Conference on Epilepsy and Society, sponsored by the International Bureau for Epilepsy (IBE) will take place October 15–17 in the World Trade Center Marseille Provence, located at the heart of Marseille, France. For more information, go to http://www.epilepsyandsociety.org/

Epilepsy at the Cutting Edge

This international meeting, celebrating the ongoing contributions of Fred and Eva Andermann, will address the genetics of epilepsy and epilepsy surgery. The meeting will be held at the Montreal Neurological Institute and Hospital, Montreal, Canada on October 23–25, 2008. Information is available at http://www.mni.mcgill.ca.

5th Latin American Epilepsy Congress

The 5th Congreso Latinoamericano de Epilepsia will take place in Montevideo, Uruguay on November 5–8, 2008. Jointly sponsored by the ILAE and IBE, the organizing committee is headed by A. Scaramelli (Uruguay), L. Núñez Orozco (Mexico), and S. Moshé (USA). Abstracts are due by May 31, 2008; pre-meeting registration deadline is September 5, 2008. For more information, contact: montevideo@epilepsycongress.org or go to http://www.epilepsymontevideo2008.org/committees.html.

2nd Biennial North American Regional Epilepsy Congress

The American Epilepsy Society will host the 2nd Biennial North American Regional Epilepsy Congress at their 62nd Annual Meeting, 5–9 December, 2008, in Seattle, WA, USA. For more information go to http://www.aesnet.org/go/meetings-and-events/annual-meeting.
GRAY MATTER

CALENDAR OF MEETINGS

July–August 2008
❑ Venice Epilepsy Summer School, 7th
  International Course: Bridging Basic with
  Clinical Epileptology – 3
  28 July–8 August
  Venice, Italy
  email: epilepsysummercourse@univiu.org
  http://www.epilearn.eu/summer_course/third/index.html

August–September 2008
❑ 2nd Baltic Sea Summer School on Epilepsy
  31 August–4 September
  Copenhagen, Denmark
  http://www.epilepsy-academy.org

September 2008
❑ 8th European Congress on Epileptology
  21–25 September
  Berlin, Germany
  http://www.epilepsyberlin2008.org

October 2008
❑ 11th European Conference on Epilepsy & Society
  (IBE)
  15–17 October
  Marseille, France
  http://www.epilepsyandsociety.org/conference_
  programme/conference_programme.html

❑ The Fred and Eva Andermann Meeting: Epilepsy
  at the Cutting Edge
  23–25 October
  Montreal, Canada
  http://www.mni.mcgill.ca

❑ 19th International Symposium on the Autonomic
  Nervous System
  29 October–1 November
  Kauai, Hawaii, U.S.A
  http://www.americanautonomicsociety.org

November 2008
❑ 5th Latin American Epilepsy Congress (ILAE &
  IBE)
  5–8 November
  Montevideo, Uruguay
  http://www.epilepsymontevideo2008.org

December 2008
❑ 2008 American Epilepsy Society Annual Meeting
  5–9 December
  Seattle, Washington, U.S.A
  http://www.aesnet.org/go/meetings-and-events/
  annual-meeting