Recent and future advances in the treatment of status epilepticus

Felix Rosenow and Susanne Knake

Therapeutic Advances in
Neurological Disorders

[2008] 1(1) 25–32

DOI: 10.1177/
1756285608094263

© SAGE Publications 2008
Los Angeles, London,
New Delhi and Singapore

Abstract: Status epilepticus (SE) is one of the most frequent neurological emergencies with an incidence of 20/100,000 per year and a mortality between 3% and 40% depending on etiology, age, SE type and duration. Generalized convulsive forms of SE (GTCSE), in particular, require aggressive treatment. Presently, only 55–80% of cases of GTCSE are controlled by initial therapy. Therefore, there is a need for new options for the treatment of SE. Here we review the current standard treatment including recent advances and provide a summary of preclinical and clinical data regarding treatment options which may become available in the near future. The initial treatment of SE usually consists of a benzodiazepine (preferably lorazepam 0.1 mg/kg) followed by phenytoin or fosphenytoin or valproic acid (where approved for SE therapy). With intravenous formulations of levetiracetam, available since 2006, and lacosamide, which is expected for autumn of 2008, new treatment options have become available, that should be evaluated in prospective controlled trials. If SE remains refractory, the induction of general anaesthesia using propofol, midazolam, thiopental, or pentobarbital is warranted in GTCSE.

Keywords: status epilepticus, antiepileptic drugs, lorazepam, levetiracetam, lacosamide

Introduction

Status epilepticus (SE) is one of the major neurological emergencies with an incidence of about 20/100,000 for the caucasian population in industrialized countries [Chin *et al.* 2006; Vignatelli *et al.* 2005, 2003; Knake *et al.* 2001; Coeytaux *et al.* 2000; Jallon *et al.* 1999]. SE has usually been defined as a single clinical seizure lasting more than 30 min or repeated seizures over a period of more than 30 min without intervening recovery of consciousness [Knake *et al.* 2001; DeLorenzo *et al.* 1995; Epilepsy Foundation of America's Working Group, 1993; Hauser, 1990].

However, in clinical practice, a generalized tonic-clonic seizure lasting for more than 5–10 min would usually be considered as SE and should be treated as such [Lowenstein and Alldredge, 1998, 1993]. The etiology of SE is heterogeneous and age dependent. The most common causes in children are febrile seizures or infections with fever, accounting for more than 52% of all pediatric cases. Remote symptomatic causes and low antiepileptic drug (AED) levels also account for a significant percentage of cases in children.

A much different picture emerges in the adult population. The major causes are remote symptomatic causes such as acute cerebrovascular accidents, hypoxia, metabolic causes and low AED levels [Knake *et al.* 2001; Hesdorffer *et al.* 1998; DeLorenzo *et al.* 1995].

SE is associated with short-term case fatality rates of around 20% (3–39%) [Rosenow *et al.* 2007; Vignatelli *et al.* 2003; Wu *et al.* 2002; Rosenow *et al.* 2002; Knake *et al.* 2001; Tomson, 2000; Kaplan, 2000; Fountain, 2000; Coeytaux *et al.* 2000; Lowenstein and Alldredge, 1998; Hesdorffer *et al.* 1998; Logroscino *et al.* 1997; DeLorenzo *et al.* 1995; Hauser, 1990]. Main predictors of case fatality are age, the etiology of SE (especially anoxia), severity of the underlying disease and the duration of SE [Garzon *et al.* 2003; Wu *et al.* 2002; Lowenstein and Alldredge, 1998; Towne *et al.* 1994; Hauser, 1990]. Patients over the age of 60 with a severe underlying disease (such as acute stroke or anoxia) have the highest risk of SE-associated mortality. Effective treatment should be initiated as soon as possible in patients with SE.

Correspondence to:

Felix Rosenow, MD
Interdisciplinary Epilepsy
Center Marburg
Department of Neurology
Philipps-University
Marburg, Rudolf-
Bultmann-Str. 8, 35033
Marburg, Germany
[rosenow@med.
uni-marburg.de](mailto:rosenow@med.uni-marburg.de)

Susanne Knake
Interdisciplinary Epilepsy
Center Marburg
Department of Neurology
Philipps-University
Marburg, Marburg
Germany

Current standard treatment of SE

There are a number of different national and European guidelines for the treatment of SE [Minicucci *et al.* 2006; Meierkord *et al.* 2006; Epilepsy Foundation of America's Working Group, 1993]. The main aims of treatment are (a) to support vital functions, (b) to identify and treat causal or precipitating factors, and (c) to terminate ictal activity. The first priority is to ensure that the airways are clear and that vital functions are maintained. Cardio-respiratory function should be checked and oxygen administered (6l/min). Intravenous (IV) access should be established so that blood can be taken to determine levels of glucose, electrolytes and drugs, to check liver and kidney function, and blood count and to give the anticonvulsant of choice. The aggressiveness of therapy and the drug chosen for treatment after a benzodiazepine (preferably lorazepam (LZP)) is given as first-line treatment depends on the SE type (e.g., generalized tonic clonic *vs* absence SE), the age, the comorbidity and the prognosis of the patient. Before IV treatment is initiated the differential diagnosis, especially the possibility of psychogenic or hypoglycemic status, should be considered.

Initial treatment of SE

Out of hospital: There is evidence that the administration of rectal diazepam (DZP) by trained lay persons, is effective in the control of acute repetitive seizures [Dreifuss *et al.* 1998]. A prospective, randomized, placebo-controlled study of GTCSE showed that the out-of-hospital use of benzodiazepines by paramedics was superior to placebo [Alldredge *et al.* 2001]. LZP (2 mg), DZP (5 mg), or placebo were initially given. A second identical dose was administered if convulsions continued after four minutes. SE was terminated on admission to the hospital in 59.9% of cases treated with LZP, in 42.6% of those treated with DZP, and in 21.1% of the patients treated with placebo. Complications (hypotension, cardiac arrhythmia, and need for respiratory support) were less frequent in the LZP (10.6%) and DZP (10.3%) groups as compared to the placebo group (22.5%). Furthermore, short-term case fatality rates were lower in the benzodiazepine-groups (LZP: 7.7%, DZP: 4.5%) compared to placebo (15.7%). It had previously been shown by the same group that the probability to control GTCSE with

initial therapy decreases with increasing SE-duration at initiation of therapy [Lowenstein and Alldredge, 1993]. If treatment was initiated within one hour, the control rate was approximately 80%. If therapy was started two hours or more after the onset, the control rate dropped to only 40–50%. In conclusion, in GTCSE a sufficient dose of a benzodiazepine (preferably 2–4 mg of LZP) should be given as soon as possible by trained paramedics or emergency doctors. Unfortunately, despite existing evidence, LZP is not approved for the treatment of SE in many countries.

On admission to hospital Once the patient is admitted, LZP should be given IV up to a total dose of 0.1 mg/kg, considering doses/timing of benzodiazepines already given out of hospital (5 mg DZP is equivalent to 1 mg LZP). It is probably less important to consider previously administered midazolam because of its short half-life. Several studies including the one by Alldredge *et al.* [2001] (described in the section above) have compared LZP to DZP in the treatment of SE. Leppik *et al.* [1983] compared LZP and DZP in 79 patients with 81 episodes of different types of SE. LZP was effective in 89% of the episodes, and DZP in 76% – a nonsignificant but potentially relevant difference. The time to onset of action and the frequency of adverse events was similar in both groups. LZP has been found to be nonsignificantly superior in each of the available comparative studies; a recent Cochrane review including eleven studies on SE concluded that LZP was superior to DZP or phenytoin in the initial treatment of established SE [Prasad *et al.* 2005]. Because LZP is less lipophilic, it has a smaller volume of distribution and a longer distribution half-life (12 h) than DZP (15–30 min), and therefore a potentially longer anticonvulsive effect [Treiman *et al.* 1998; Greenblatt and Divoll, 1983]. Soluble preparations of LZP need to be stored cooled, which is a practical disadvantage. However, efficacy can be maintained for at least three days if not sufficiently cooled [Alldredge *et al.* 2001].

Traditionally, the initial rapidly acting benzodiazepine was followed by a dose of 18 mg/kg of IV phenytoin given at a maximal infusion rate of 50 mg/minute [Delgado-Escueta *et al.* 1982]. Only relatively recently a controlled study investigating the treatment of GTCSE addressed the treatment options on arrival at hospital [Treiman *et al.* 1998]. The authors divided GTCSE in

two groups: 'overt SE' (with clearly visible convulsions) and 'subtle SE' (with only subtle motor manifestations as a sequel of electromechanic decoupling, usually occurring in the later stages of GTCSE). They compared the SE control rates 20 min after initiation of four different therapies: DZP (0.15 mg/kg) followed by phenytoin (18 mg/kg); LZP (0.1 mg/kg); phenobarbital (15 mg/kg); or phenytoin (18 mg/kg) alone. Overt SE was controlled within 20 min after initiation of therapy with LZP in 64.9% as compared to DZP followed by phenytoin (55.8%), phenobarbital (58.2%) and phenytoin alone (42.6%). The only treatment significantly worse than LZP alone was phenytoin alone. Interestingly, phenobarbital was most effective in the smaller group of patients with subtle SE – with low control rates of 24.2% as compared to 17.9 (LZP), 8.3% (DZP plus phenytoin), and 7.7% (phenytoin alone). The frequency of hypotension and respiratory insufficiency was similar across the groups [Treiman *et al.* 1998].

Phenytoin solution can lead to severe tissue damage, especially if injected paravenously [Rao *et al.* 1988; Kilarski *et al.* 1984]. Due to its very alkaline pH of 12, even IV application can result in phlebitis and, in more severe cases, the so called 'purple glove syndrome' in at least 1.5% of patients [Burneo *et al.* 2001; O'Brien *et al.*

1998; Jamerson *et al.* 1994]. Fosphenytoin is a disodium phosphate ester of 3-hydroxy-methyl-5,5 diphenylhydantoin, which is rapidly and completely converted to phenytoin (conversion half-life 8–15 min). The ready-mixed solution is buffered to a pH of 8.6–9 and can be given IV or intramuscularly (IM). However, IM application is not recommended during SE, because absorption is unreliable and may take more time. Local toxicity is clearly decreased compared to phenytoin [Ramsay *et al.* 1995; Jamerson *et al.* 1994]. Fosphenytoin is given at a rate of 100–150 mg/min, compared to 50 mg/min for phenytoin. However, maximal plasma concentrations achieved are approximately 15% lower than with phenytoin [Browne *et al.* 1996; Eldon and Loewen, 1993], and in rats, the brain tissue concentrations reached with fosphenytoin are lower than those achieved using equivalent doses of phenytoin [Walton *et al.* 1999]. In conclusion, fosphenytoin is preferable to phenytoin for IV use.

If possible and especially when there is delayed recovery, clinical treatment success should be confirmed by EEG because it has been reported that up to 14% of patients treated for GTCSE remain in nonconvulsive SE after the convulsions are clinically controlled [DeLorenzo *et al.* 1998] (Table 1).

Table 1. Standard and alternative treatments in generalized convulsive status epilepticus (adapted from Rosenow *et al.* 2002).

	Standard dose suggested	Alternative dose suggested
Initial SE	Lorazepam (0.1 mg/kg at 2 mg/min)	Diazepam (10–20 mg at 2–5 mg/min in adults; 0.25–0.5 mg/kg at 2–5 mg/min in children); Clonazepam (up to 0.025 mg/kg; 1 mg/5 min)
Continued SE	Phenytoin (15–20 mg/kg not exceeding 50 mg/min in adults; 20 mg/kg at 1 mg/kg/min in children). Slow infusion rate if hypotension occurs	Fosphenytoin (in adults, 15–20 mg/kg of phenytoin equivalents at 100–150 mg/min); Valproate* (20–25 mg/kg over 5–10 min followed by 2 mg/kg/h)
Refractory SE	Phenobarbital (10–20 mg/kg at 100 mg/min)	Midazolam (LD: 0.15–0.2 mg/kg, MD: 0.1–0.4 mg/kg/h) (93, 96); Propofol (LD: 2 mg/kg, MD: 6–12 mg/kg/h)
>60 min	Pentobarbital (LD: 12 mg/kg, MD: 5 mg/kg/h or by EEG) Thiopental (in adults, 100–250 mg bolus over 20 s then further 50 mg boluses every 2–3 min until seizure control, followed by infusion to maintain burst suppression, usually at 3–5 mg/kg/h)	
LD, loading dose; MD, maintenance dose; SE, status epilepticus		
*Currently only approved for the treatment of SE in Norway and Germany.		

Refractory SE

Refractory status epilepticus (RSE) is defined as SE that has failed to respond to first and second-line anticonvulsant drugs [Bleck, 2005; Claassen *et al.* 2002; Treiman *et al.* 1998; Bleck, 1993] and occurs in up to 44% of all patients with SE [Stecker *et al.* 1998; Lowenstein and Alldredge 1998; Krishnamurthy and Drislane, 1996; Yaffe and Lowenstein, 1993]. The mortality of RSE is at least 16–23% and again depends on age and etiology [Rossetti *et al.* 2005; Holtkamp *et al.* 2005; Claassen *et al.* 2002; Mayer *et al.* 2002]. Its treatment remains a challenge and has not been investigated in prospective trials so far. In general, RSE is treated with coma induction using anesthetics such as propofol, or midazolam or barbiturates (pentobarbital or thiopental).

A meta-analysis on the treatment of 193 patients with RSE that were treated with pentobarbital, propofol, or midazolam suggested that pentobarbital was superior regarding treatment success and prevention of breakthrough seizures but was associated with more side effects such as hypotension. There was no difference between all three agents in terms of short-term case fatality, which was between 40% and 50% [Claassen *et al.* 2002]. Other anesthetics, such as isoflurane, ketamine, or lidocaine have been used in single patients and may be an option if SE remains refractory [Rossetti, 2007; Mirsattari *et al.* 2004; Sheth and Gidal, 1998].

New options

Valproic acid has been used IV in SE for more than 20 years; however, only one randomized study has been performed comparing phenytoin alone (an inferior treatment) against valproate, but without a conclusive statistical difference (one-sided *t*-tests were used) [Misra *et al.* 2006]. Despite the lack of good class I evidence, IV valproate (ivVPA) has recently been approved for the treatment of SE in Norway (in 2004) for SE, in adults and Germany (in 2007) as third choice drug for generalized convulsive SE, as second choice for simple and complex partial SE and as a first choice in absence SE. The approval was based on more than 300 'well-documented' cases of SE treated with ivVPA published in a number of case series [Olsen *et al.* 2007; Velioglu and Gazioglu, 2007; Limdi *et al.* 2005; Uberall *et al.* 2000; Sinha and Naritoku, 2000; Venkataraman and Wheless,

1999; Czapinski and Terczynski, 1998], the interaction, especially with phenobarbital, and the rare occurrences of pancreatitis are problematic [Grosse *et al.* 1999]. Furthermore, VPA should not be administered to patients with mitochondrial disease or severe liver disease [Uusimaa *et al.* 2008; Rosenow *et al.* 2002].

Future options

After a long interval during which many novel AEDs reached the market but were not made available for IV use, IV levetiracetam was approved in 2006 for patients who cannot take their medication orally. In 2008, lacosamide will be the first AED to be approved simultaneously as an oral and IV formulation. Both compounds will not be approved for the use in SE.

Levetiracetam

Levetiracetam (LEV) is a SV2A-ligand and inhibits high-voltage-gated calcium currents, selectively involving the N-type-calcium channels [Lukyanetz *et al.* 2002]. LEV has been studied in several animal models of SE. Animal studies support the anticonvulsive effect of LEV in SE showing that LEV prevented, diminished or aborted seizures in rats with self-sustained SE and that LEV may enhance the effect of benzodiazepines [Mazarati *et al.* 2004]. However, other groups could not confirm the anticonvulsive effect in rats during SE but suggested neuroprotective properties of LEV. In a rat model of self-sustaining limbic SE after two hours of stimulation of the perforant path, LEV administration did not terminate seizures or have any significant effect on spike frequency but improved biochemical function, indicating that LEV might protect against mitochondrial dysfunction during SE in rats [Gibbs and Cock, 2007; Gibbs *et al.* 2006].

In healthy humans, bioequivalence of oral and IV administered doses of 1500–4000 mg LEV has been shown [Ramael *et al.* 2006a, b]. A steady state was reached after 48 h for oral and IV application [Ramael *et al.* 2006a]. Rapid infusion rates of up to 4000 mg/15 min or 2500 mg/5 min have been well tolerated, with few and minor side effects affecting the central nervous system such as somnolence or dizziness. No serious adverse events occurred [Ramael *et al.* 2006a, b].

Clinical data on the treatment of SE in humans are sparse: there are a few case reports [Schulze-Bonhage *et al.* 2007] and one small

clinical series [Knake *et al.* 2008] on the treatment of SE with IV LEV. Data so far suggest that LEV may be an effective and well-tolerated treatment for SE. However, LEV is not approved for the treatment of SE and further prospective controlled evaluation in a larger number of patients is warranted.

Lacosamide (formerly SP927, harkoseride, ADD-234037)

Lacosamide (LCM) selectively affects sodium channel slow but not fast inactivation and so reduces the long-term availability of sodium channels. Furthermore, it modulates the collapsin response mediator protein 2 (CRMP-2). It is currently not clear if this mode of action contributes to the anticonvulsive effects of LCM [Doty *et al.* 2007]. Lacosamide has been studied in different SE models. In self-sustained SE evoked by 60 min of electrical stimulation of the perforant path, LCM (50 mg/kg) was compared to DZP (10 mg/kg), phenytoin (50 mg/kg), and vehicle. Drugs were injected 10 min after the end of the stimulation and all reduced seizure duration and time to last seizure significantly compared to vehicle, LCM was most effective [Stohr *et al.* 2006]. In a second study, LCM was injected 10 min after the initiation of the status by electrical stimulation of 30 min duration. LCM significantly reduced neuronal loss in CA1 and CA3 as compared to vehicle [Stohr and Wasterlain, 2006]. Furthermore, LCM showed efficacy in two models of chemically-induced SE. In the cobalt/homocysteine-induced model, LCM protected against GTC seizures and in the lithium chloride/pilocarpine model neuroprotective effects were seen [Stohr *et al.* 2007; Bialer *et al.* 2007; Stohr *et al.* 2003].

In probands, bioequivalence with regards to the oral application was demonstrated after injection of 200 mg over 15, 30, or 60 min. Sleepiness, dizziness, and perioral hypesthesia were the most common adverse events. An initial IV replacement trial in 60 patients showed that LCM was well tolerated when given over 30 or 60 min [Biton *et al.* 2008]. Subsequently, during a phase 3 extension study (SP755) 160 patients with focal epilepsy received IV replacement of their oral dose, usually 400–600 mg/day (200–800 mg). The daily dose was given in two doses administered within 10, 15, or 30 min. Headache occurring in 5–8%, dizziness in 5–8%, somnolence 0–10%, and diplopia (0–5%) were the most frequent adverse events.

One serious adverse event, a bradycardia of 4 min duration, occurred during the second but not first 15-min infusion, and was interpreted to be caused by a vasovagal event (Krauss *et al.* 2007). It was concluded that the IV application was dose-equivalent and of similar tolerability to the oral formulation [Doty *et al.* 2007].

Based on these data, LCM is certainly a promising candidate for clinical evaluation in the treatment of SE.

Problems with, and designs for, future trials

The lack of evidence from controlled double blind trials of SE treatment has several reasons: (a) it is usually not possible to obtain informed consent, which under the current EU directive (2001/20/EC, 4.4.2001) renders it practically impossible to include patients in the European Union; (b) the potential economic gain for the pharmaceutical industry from developing drugs for SE is low, even though the impact of SE on the population is substantial; (c) SE is an emergency situation with little time to establish even the diagnosis and underlying aetiology, and treatment is frequently initiated outside the hospital; (d) Current treatment controls GTCSE in 64–80% of cases [Misra *et al.* 2006; Treiman, 1998]. In order to demonstrate that a new drug is 10% more effective or equally effective as current standard treatment, more than 800 patients would need to be included. Should these problems be overcome, a trial design should consider: (a) a prospective randomized assignment to treatment groups; (b) double-blind parallel group designs, and (c) unambiguous operational definitions of SE and treatment success. EEG monitoring is important in this respect. Patients with generalized tonic clonic SE, complex partial SE, and simple partial SE with motor signs should be included in such a trial, using a stratified randomization procedure. Patients with absence status and simple partial status without motor signs should be excluded. Since the study by Alldredge *et al.*, it is clear that LCP is more efficacious and safer than placebo and the trial by Treiman *et al.* demonstrated that there are three equally effective standard treatments. Therefore, placebo groups are no longer ethically acceptable, every patient included needs to receive one of these standard treatments [Alldredge *et al.* 2001; Treiman, 1998; Treiman *et al.* 1998]. For a life-threatening disorder such as SE a 10% improvement in success rate or clear

demonstration of noninferiority for substances that are better tolerated (e.g., fosphenytoin or valproate *vs* phenytoin) would be clinically meaningful. Such results need to be supported with substantial statistical power [Treiman, 1998]. Therefore, in future studies, no more than two treatment arms should be compared. One possibility would be LZP plus either fosphenytoin or a new agent (e.g., LCM or LEV).

Conflict of interest statement

None declare.

References

- Treatment of convulsive status epilepticus. (1993) Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. *JAMA* 270: 854–859.
- Allredge, B.K., Gelb, A.M., Isaacs, S.M., Corry, M.D., Allen, F., Ulrich, S. *et al.* (2001) A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med* 345: 631–637.
- Bialer, M., Johannessen, S.I., Kupferberg, H.J., Levy, R.H., Perucca, E. and Tomson, T. (2007) Progress report on new antiepileptic drugs: a summary of the Eighth Eilat Conference (EILAT VIII). *Epilepsy Res* 73: 1–52.
- Biton, V., Rosenfeld, W.E., Whitesides, J., Fountain, N.B., Vaiciene, N and Rudd, G.D. (2008) Intravenous lacosamide as replacement for oral lacosamide in patients with partial-onset seizures. *Epilepsia* 49: 418–424.
- Bleck, T.P. (1993) Advances in the management of refractory status epilepticus. *Crit Care Med*. 21: 955–957.
- Bleck, T.P. (2005) Refractory status epilepticus. *Curr Opin Crit Care* 11: 117–120.
- Browne, T.R., Kugler, A.R. and Eldon, M.A. (1996) Pharmacology and pharmacokinetics of fosphenytoin. *Neurology* 46: S3–S7.
- Burneo, J.G., Anandan, J.V. and Barkley, G.L. (2001) A prospective study of the incidence of the purple glove syndrome. *Epilepsia* 42: 1156–1159.
- Chin, R.F., Neville, B.G., Peckham, C., Bedford, H., Wade, A. and Scott, R.C. (2006) Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. *Lancet* 368: 222–229.
- Claassen, J., Hirsch, L.J., Emerson, R.G. and Mayer, S.A. (2002) Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia* 43: 146–153.
- Coeytaux, A., Jallon, P., Galobardes, B. and Morabia, A. (2000) Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). *Neurology* 55: 693–697.
- Czapinski, P. and Terczynski, A. (1998) [Intravenous valproic acid administration in status epilepticus]. *Neurol Neurochir Pol* 32: 11–22.
- DeLorenzo, R.J., Pellock, J.M., Towne, A.R. and Boggs, J.G. (1995) Epidemiology of status epilepticus. *J Clin Neurophysiol* 12: 316–325.
- DeLorenzo, R.J., Waterhouse, E.J., Towne, A.R., Boggs, J.G., Ko, D., DeLorenzo, G.A. *et al.* (1998) Persistent nonconvulsive status epilepticus after the control of convulsive status epilepticus. *Epilepsia* 39: 833–840.
- Doty, P., Rudd, G.D., Stoehr, T. and Thomas, D. (2007) Lacosamide. *Neurotherapeutics* 4: 145–148.
- Dreifuss, F.E., Rosman, N.P., Cloyd, J.C., Pellock, J.M., Kuzniecky, R.I., Lo, W.D. *et al.* (1998) A comparison of rectal diazepam gel and placebo for acute repetitive seizures. *N Engl J Med* 338: 1869–1875.
- Eldon, M.A. and Loewen, G. (1993) Pharmacokinetics and tolerance of fosphenytoin and phenytoin administration intravenously to healthy subjects. *Can J Neurol Sci* 20: 5180.
- Fountain, N.B. (2000) Status epilepticus: risk factors and complications. *Epilepsia* 41(Suppl 2): S23–S30.
- Delgado-Escueta, A.V., Wasterlain, C., Treiman, D.M. and Porter, R.J. (1982) Current concepts in neurology: management of status epilepticus. *N Engl J Med* 306: 1337–1340.
- Garzon, E., Fernandes, R.M. and Sakamoto, A.C. (2003) Analysis of clinical characteristics and risk factors for mortality in human status epilepticus. *Seizure* 12: 337–345.
- Gibbs, J.E. and Cock, H.R. (2007) Administration of levetiracetam after prolonged status epilepticus does not protect from mitochondrial dysfunction in a rodent model. *Epilepsy Res* 73: 208–212.
- Gibbs, J.E., Walker, M.C. and Cock, H.R. (2006) Levetiracetam: antiepileptic properties and protective effects on mitochondrial dysfunction in experimental status epilepticus. *Epilepsia* 47: 469–478.
- Greenblatt, D.J. and Divoll, M. (1983) Diazepam versus lorazepam: relationship of drug distribution to duration of clinical action. *Adv Neurol* 34: 487–491.
- Grosse, P., Rusch, L. and Schmitz, B. (1999) Pancreatitis complicating treatment of status epilepticus with intravenous valproate. *Epilepsia* 40: S267.
- Hauser, W.A. (1990) Status epilepticus: epidemiologic considerations. *Neurology* 40: 9–13.
- Hesdorffer, D.C., Logroscino, G., Cascino, G., Annegers, J.F. and Hauser, W.A. (1998) Incidence

- of status epilepticus in Rochester, Minnesota, 1965–1984. *Neurology* 50: 735–741.
- Holtkamp, M., Othman, J., Buchheim, K. and Meierkord, H. (2005) Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. *J Neurol Neurosurg Psychiatry* 76: 534–539.
- Jallon, P., Coeytaux, A., Galobardes, B. and Morabia, A. (1999) Incidence and case-fatality rate of status epilepticus in the Canton of Geneva. *Lancet* 353: 1496.
- Jamerson, B.D., Dukes, G.E., Brouwer, K.L., Donn, K.H., Messenheimer, J.A. and Powell, J.R. (1994) Venous irritation related to intravenous administration of phenytoin versus fosphenytoin. *Pharmacotherapy* 14: 47–52.
- Kaplan, P.W. (2000) Prognosis in nonconvulsive status epilepticus. *Epileptic Disord* 2: 185–193.
- Kilariski, D.J., Buchanan, C. and Von Behren, L. (1984) Soft-tissue damage associated with intravenous phenytoin. *N Engl J Med* 311: 1186–1187.
- Knake, S., Gruener, J., Hattmer, K., Klein, K.M., Bauer, S., Oertel, W.H. *et al.* (2008) Intravenous levetiracetam in the treatment of benzodiazepine refractory status epilepticus. *J Neurol Neurosurg Psychiatry* 79: 588–589.
- Knake, S., Rosenow, F., Vescovi, M., Oertel, W.H., Mueller, H.H., Wirbatz, A. *et al.* (2001) Incidence of status epilepticus in adults in Germany: a prospective, population-based study. *Epilepsia* 42: 714–718.
- Krauss, G., Ben-Menache, M.E., Mameniskiene, R., Vaiciene, N., Brock, M., Whitesides, J. *et al.* (2007). Intravenous lacosamide as replacement for oral lacosamide in subjects with partial seizure onset: a multicenter, open-label, inpatient trial examining safety and tolerability of 10- and 15-minute infusions. Poster presented at the Annual Meeting of the American Epilepsy Society.
- Krishnamurthy, K.B. and Drislane, F.W. (1996) Relapse and survival after barbiturate anesthetic treatment of refractory status epilepticus. *Epilepsia* 37: 863–867.
- Leppik, I.E., Derivan, A.T., Homan, R.W., Walker, J., Ramsay, R.E. and Patrick, B. (1983) Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA* 249: 1452–1454.
- Limdi, N.A., Shimpi, A.V., Faught, E., Gomez, C.R. and Burneo, J.G. (2005) Efficacy of rapid IV administration of valproic acid for status epilepticus. *Neurology* 64: 353–355.
- Logroscino, G., Hesdorffer, D.C., Cascino, G., Annegers, J.F. and Hauser, W.A. (1997) Short-term mortality after a first episode of status epilepticus. *Epilepsia* 38: 1344–1349.
- Lowenstein, D.H. and Alldredge, B.K. (1993) Status epilepticus at an urban public hospital in the 1980s. *Neurology* 43: 483–488.
- Lowenstein, D.H. and Alldredge, B.K. (1998) Status epilepticus. *N Engl J Med* 338: 970–976.
- Lukyanetz, E.A., Shkryl, V.M. and Kostyuk, P.G. (2002) Selective blockade of N-type calcium channels by levetiracetam. *Epilepsia* 43: 9–18.
- Mayer, S.A., Claassen, J., Lokin, J., Mendelsohn, F., Dennis, L.J. and Fitzsimmons, B.F. (2002) Refractory status epilepticus: frequency, risk factors, and impact on outcome. *Arch Neurol* 59: 205–210.
- Mazarati, A.M., Baldwin, R., Klitgaard, H., Matagne, A. and Wasterlain, C.G. (2004) Anticonvulsant effects of levetiracetam and levetiracetam-diazepam combinations in experimental status epilepticus. *Epilepsy Res* 58: 167–174.
- Meierkord, H., Boon, P., Engelsens, B., Göcke, K., Shorvon, S., Tinuper, P. *et al.* (2006) EFNS guideline on the management of status epilepticus. *Eur J Neurol* 13: 445–450.
- Minicucci, F., Muscas, G., Perucca, E., Capovilla, G., Vigeveno, F. and Tinuper, P. (2006) Treatment of status epilepticus in adults: guidelines of the Italian League against Epilepsy. *Epilepsia* 47(Suppl 50): 9–15.
- Mirsattari, S.M., Sharpe, M.D. and Young, G.B. (2004) Treatment of refractory status epilepticus with inhalational anesthetic agents isoflurane and desflurane. *Arch Neurol* 61: 1254–1259.
- Misra, U.K., Kalita, J. and Patel, R. (2006) Sodium valproate vs phenytoin in status epilepticus: a pilot study. *Neurology* 67: 340–342.
- O'Brien, T.J., Cascino, G.D., So, E.L. and Hanna, D.R. (1998) Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin. *Neurology* 51: 1034–1039.
- Olsen, K.B., Tauboll, E. and Gjerstad, L. (2007) Valproate is an effective, well-tolerated drug for treatment of status epilepticus/serial attacks in adults. *Acta Neurol Scand Suppl* 187: 51–54.
- Prasad, K., Al Roomi, K., Krishnan, P.R. and Sequeira, R. (2005) Anticonvulsant therapy for status epilepticus. *Cochrane Database Syst Rev* (4): CD003723.
- Ramael, S., Daoust, A., Otoul, C., Toublanc, N., Troenaru, M., Lu, Z.S. *et al.* (2006a) Levetiracetam intravenous infusion: a randomized, placebo-controlled safety and pharmacokinetic study. *Epilepsia* 47: 1128–1135.
- Ramael, S., De, S.F., Toublanc, N., Otoul, C., Boulanger, P., Riethuisen, J.M. *et al.* (2006b) Single-dose bioavailability of levetiracetam intravenous infusion relative to oral tablets and multiple-dose pharmacokinetics and tolerability of levetiracetam intravenous infusion compared with placebo in healthy subjects. *Clin Ther* 28: 734–744.
- Ramsay, R.E., Philbrook, B. and Martinez, D. (1995) A double-blind, randomized safety comparison of

- rapidly infused intravenous loading doses of fosphenytoin vs phenytoin. *Epilepsia* 36: S90.
- Rao, V.K., Feldman, P.D. and Dibbell, D.G. (1988) Extravasation injury to the hand by intravenous phenytoin. Report of three cases. *J Neurosurg* 68: 967–969.
- Rosenow, F., Arzimanoglou, A. and Baulac, M. (2002) Recent developments in treatment of status epilepticus: a review. *Epileptic Disord* 4(Suppl 2): S41–S51.
- Rosenow, F., Hamer, H.M. and Knake, S. (2007) The epidemiology of convulsive and nonconvulsive status epilepticus. *Epilepsia* 48(Suppl 8): 82–84.
- Rossetti, A.O. (2007) Which anesthetic should be used in the treatment of refractory status epilepticus? *Epilepsia* 48(Suppl 8): 52–55.
- Rossetti, A.O., Logroscino, G. and Bromfield, E.B. (2005) Refractory status epilepticus: effect of treatment aggressiveness on prognosis. *Arch Neurol* 62: 1698–1702.
- Schulze-Bonhage, A., Hefft, S. and Oehl, B. (2007) Termination of complex partial status epilepticus by intravenous levetiracetam - a case report. *J Neurol Neurosurg Psychiatry* Epub ahead, Mar 2007; doi:10.1136/jnnp.2006.113951.
- Sheth, R.D. and Gidal, B.E. (1998) Refractory status epilepticus: response to ketamine. *Neurology* 51: 1765–1766.
- Sinha, S. and Naritoku, D.K. (2000) Intravenous valproate is well tolerated in unstable patients with status epilepticus. *Neurology* 55: 722–724.
- Stecker, M.M., Kramer, T.H., Raps, E.C., O'Meeghan, R., Dulaney, E. and Skaar, D.J. (1998) Treatment of refractory status epilepticus with propofol: clinical and pharmacokinetic findings. *Epilepsia* 39: 18–26.
- Stohr, T., Baldwin, R., Walton, N. and Westerlain, C. (2003) SPM 927 is Anticonvulsive and neuroprotective in rat models for self-sustaining status epilepticus. Poster presented at the American Epilepsy Society meeting 2003 in Boston. Ref Type: Abstract.
- Stohr, T., Krause, E. and Selve, N. (2006) Lacosamide displays potent antinociceptive effects in animal models for inflammatory pain. *Eur J Pain* 10: 241–249.
- Stohr, T., Kupferberg, H.J., Stables, J.P., Choi, D., Harris, R.H., Kohn, H. *et al.* (2007) Lacosamide, a novel anti-convulsant drug, shows efficacy with a wide safety margin in rodent models for epilepsy. *Epilepsy Res* 74: 147–154.
- Stohr, T. and Westerlain, C. (2006) Lacosamide in vitro and in vivo animal models for Neuroprotection. Poster presented at the American Epilepsy Society Meeting 2006. Ref Type: Abstract.
- Tomson, T. (2000) Mortality in epilepsy. *J Neurol* 247: 15–21.
- Towne, A.R., Pellock, J.M., Ko, D. and DeLorenzo, R.J. (1994) Determinants of mortality in status epilepticus. *Epilepsia* 35: 27–34.
- Treiman, D.M. (1998) Clinical trials for status epilepticus. *Adv Neurol* 76: 173–178.
- Treiman, D.M., Meyers, P.D., Walton, N.Y., Collins, J.F., Colling, C., Rowan, A.J. *et al.* (1998) A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med* 339: 792–798.
- Uberall, M.A., Trollmann, R., Wunsiedler, U. and Wenzel, D. (2000) Intravenous valproate in pediatric epilepsy patients with refractory status epilepticus. *Neurology* 54: 2188–2189.
- Uusimaa, J., Hinttala, R., Rantala, H., Päiväranta, M., Herra, R., Røyttä, M. *et al.* (2008) Homozygous W748S mutation in the POLG1 gene in patients with juvenile-onset Alpers syndrome and status epilepticus. *Epilepsia*.
- Velioglu, S.K. and Gazioglu, S. (2007) Non-convulsive status epilepticus secondary to valproic acid-induced hyperammonemic encephalopathy. *Acta Neurol Scand* 116: 128–132.
- Venkataraman, V. and Wheless, J.W. (1999) Safety of rapid intravenous infusion of valproate loading doses in epilepsy patients. *Epilepsy Res* 35: 147–153.
- Vignatelli, L., Rinaldi, R., Galeotti, M., de, C.P. and D'Alessandro, R. (2005) Epidemiology of status epilepticus in a rural area of northern Italy: a 2-year population-based study. *Eur J Neurol* 12: 897–902.
- Vignatelli, L., Tonon, C. and D'Alessandro, R. (2003) Incidence and short-term prognosis of status epilepticus in adults in Bologna, Italy. *Epilepsia* 44: 964–968.
- Walton, N.Y., Uthman, B.M., El Yafi, K., Kim, J.M. and Treiman, D.M. (1999) Phenytoin penetration into brain after administration of phenytoin or fosphenytoin. *Epilepsia* 40: 153–156.
- Wu, Y.W., Shek, D.W., Garcia, P.A., Zhao, S. and Johnston, S.C. (2002) Incidence and mortality of generalized convulsive status epilepticus in California. *Neurology* 58: 1070–1076.
- Yaffe, K. and Lowenstein, D.H. (1993) Prognostic factors of pentobarbital therapy for refractory generalized status epilepticus. *Neurology* 43: 895–900.