The objective of the current paper was to review the literature and discuss the degree of evidence for various treatment strategies for status epilepticus (SE) in adults. We searched MEDLINE and EMBASE for relevant literature from 1966 to January 2005. Furthermore, the Cochrane Central Register of Controlled Trials (CENTRAL) was sought. Recommendations are based on this literature and on our judgement of the relevance of the references to the subject. Recommendations were reached by informative consensus approach. Where there was a lack of evidence but consensus was clear we have stated our opinion as good practice points.

The preferred treatment pathway for generalised convulsive status epilepticus (GCSE) is intravenous (i.v.) administration of 4 mg of lorazepam or 10 mg of diazepam directly followed by 15–18 mg/kg of phenytoin or equivalent fosphenytoin. If seizures continue for more than 10 min after first injection another 4 mg of lorazepam or 10 mg of diazepam is recommended. Refractory GCSE is treated by anaesthetic doses of midazolam, propofol or barbiturates; the anaesthetics are titrated against an electroencephalogram burst suppression pattern for at least 24 h. The initial therapy of non-convulsive SE depends on the type and the cause. In most cases of absence SE, a small i.v. dose of lorazepam or diazepam will terminate the attack. Complex partial SE is initially treated such as GCSE, however, when refractory further non-anaesthetising substances should be given instead of anaesthetics. In subtle SE i.v. anaesthesia is required.

The basic processes generating SE may be seen as a failure of the normal mechanisms that terminate seizures. Reduced inhibition and persistent excessive excitation create interactions that produce and sustain ongoing seizure activity. Pronounced excitation via glutamate analogues leads to prolongation of seizures [9] and GABA antagonists such as picrotoxin and bicuculline may also provoke SE [10], both impairing the usual mechanism by which seizures terminate. During prolonged seizure activity dynamic changes in GABA_A
receptor function has been described resulting in progressive receptor insensitivity [11]. Absence SE with 3-Hz spike-wave discharges are induced by excessive inhibition [12]. This form of SE does not lead to the neuronal injury seen with excessive excitation [13].

Search strategy
One member of the Task Force Panel (HM) searched published reports from 1966 to 2005 using the database MEDLINE and EMBASE (last search in January 2005). The search was limited to papers published in English. The subject term ‘status epilepticus’ was combined with the terms ‘controlled clinical trial’, ‘randomised controlled trial’ (RCT), ‘multicentre study’, meta analysis’ and ‘cross over study’. Furthermore, the Cochrane Central Register of Controlled Trials (CENTRAL) was sought. Finally, the websites of the World Health Organisation (WHO), the International League against Epilepsy (ILAE) and the American Neurological Association (ANA) were explored to look for additional information.

Evaluation of published literature
The evidence for therapeutic interventions (class I–IV) and the rating of recommendations (level A–C) were classified by using the definitions previously reported [14].

Methods for reaching consensus
The other members of the task force read the first draft of the recommendations and discussed changes (informative consensus approach). Where there was a lack of evidence but consensus was clear we have stated our opinion as good practice points (GPP).

Definitions
The time that has to evolve to define ongoing epileptic activity as ‘status epilepticus’ is as yet not generally agreed upon. The Commission on Classification and Terminology of the ILAE defines SE as ‘a seizure [that] persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur’ [15]. Experimental studies have shown irreversible neuronal damage after about 30 min of continuing epileptic activity [16]. Therefore, this time window has been adopted by the majority of authors [1,2,17]. On the other hand some clinical data indicate that spontaneous cessation of generalised convulsive seizures is unlikely after 5 min [18,19] and, therefore, acute treatment with anticonvulsants is required.

Consequently, Lowenstein et al. [26] have proposed an operational definition of SE that is based on a duration of 5 min [20]. Currently, clinical studies are based on 5 min [21], 10 min [6,7] or 30 min [2,22] of ongoing epileptic activity to define SE. The diagnosis of NCSE is based on a change in behaviour and/or mentation from baseline and an associated electroencephalogram (EEG) with epileptiform discharges [23]. Currently, there is no generally accepted duration of electro-clinical alterations incorporated in the diagnostic criteria of NCSE.

NCSE includes subtypes such as absence status, complex partial SE and subtle generalised SE. The latter evolves from overt GCSE and is characterised by coma and ongoing electrographic seizure activity without any or with subtle convulsive movements [6]. Absence SE with 3-Hz spike-wave discharges is a more benign type of SE and is not further considered in this paper.

An appropriate definition of refractory SE also is still missing. The failure of two [7,24] or three [25,26] anticonvulsants has been suggested in combination with a minimal duration of the condition of 1 h [7,27], 2 h [24,28] or regardless of the time that has elapsed since onset [22,26].

Results

Literature and data on treatment
Initial treatment of generalised convulsive status epilepticus
High-level evidence for the initial pharmacological treatment of GCSE has been given in three RCTs that are indicated below. In 384 patients with GCSE, intravenous (i.v.) administration of 0.1 mg/kg of lorazepam was successful in 64.9% of cases, 15 mg/kg of phenobarbital in 58.2%, and 0.15 mg/kg of diazepam followed by 18 mg/kg phenytoin in 55.8%; the efficacy of these anticonvulsants was not significantly different [6] (Class I). The same trial has shown that in pairwise comparison initial monotherapy with 18 mg/kg phenytoin is significantly less effective than administration of lorazepam. Another RCT has focussed on the pre-hospital treatment of GCSE performed by paramedics [21] (Class I). Patients were administered 2 mg of i.v. lorazepam, 5 mg of i.v. diazepam, or placebo, the injection of identical doses of benzodiazepines was repeated when seizures continued for more than 4 min. Lorazepam terminated SE in 59.1% of cases and was as effective as diazepam (42.6%). Both drugs were significantly superior to the administration of placebo (21.1%). An earlier RCT on 81 episodes of all clinical forms of SE compared i.v.
administration of 4 mg of lorazepam vs. 10 mg of diazepam, which were repeated when seizures continued or recurred after 10 min [29] (Class I). In episodes of GCSE with or without focal onset \((n = 39)\) 13 episodes responded to lorazepam after the first administration and three after the second whilst three episodes did not respond. With diazepam 14 episodes responded to the first administration and two to the second whilst four episodes did not respond.

Initial treatment of non-convulsive status epilepticus

The pharmacological treatment of subtle SE has been addressed in a RCT with 134 patients [6] (Class I). The i.v. administration of lorazepam \((0.1 \text{ mg/kg})\), diazepam \((0.15 \text{ mg/kg})\) followed by phenytoin \((18 \text{ mg/kg})\), phenobarbital \((18 \text{ mg/kg})\) and phenytoin \((18 \text{ mg/kg})\) terminated SE in 8–24% of cases only. Success rates were not significantly different between the drugs or drug combinations tested. However, key criterion for study entry was the evidence of subtle SE at the time of evaluation, regardless of prior treatment. Though not further specified, it can be assumed that in some of the patients, anticonvulsants have been administered before. Further RCT or other prospective data focusing on the treatment of subtle or other forms of NCSE are missing. Even retrospective studies usually do not address this frequent subgroup of SE.

Side effects of initial treatment of status epilepticus

Safety issues of the common initial anticonvulsants have been compared in patients with generalised convulsive SE as well as in patients with non-convulsive subtle SE [6] (Class I). In GCSE hypoventilation was observed in 10–17% of cases, hypotension in 26–34%, and cardiac arrhythmias in 2–7%. These side effects were more frequent in subtle SE and ranged between 3 and 59% of cases. Distribution of side effects was not significantly different in patients treated with lorazepam, diazepam followed by phenytoin, phenobarbital and phenytoin in overt and subtle SE. Out-of-hospital administration of benzodiazepines compared to placebo did not result in more complications such as arterial hypotension, cardiac dysrhythmia or respiratory intervention [21] (Class I). These side effects occurred in 10.6% of patients treated with lorazepam, 10.3% of patients treated with diazepam and 22.5% of patients given placebo.

Refractory status epilepticus

The rationale for treating refractory SE with anaesthetics is that prolonged electrographic seizure activity, in experimental animal models, results in brain damage [30,31]. To what extent this occurs in human SE is not known, but it is for this reason that most authorities recommend general anaesthesia to obtain burst suppression on the EEG (i.e. the absence of electrographic seizure activity) if initial therapy has not controlled the SE within 1–2 h. However, there are no studies comparing anaesthetic therapy with continuing non-anaesthetising anticonvulsants. The therapeutic decision is based on the type of SE, comorbidity and prognostic issues. This is of special relevance in patients with non-convulsive forms of SE since the risks of anaesthesia (e.g. arterial hypotension, gastroparesis, immunosuppression, etc.) may be greater than the risks of ongoing non-convulsive epileptic activity [32]. In view of the lack of controlled studies, the decision on further treatment is based on a few retrospective studies and expert opinions. Retrospective studies have analysed the further treatment options after failure of initial anticonvulsants [7]. It should be noted that treatment pathways were naturally influenced by multiple variables such as aetiology, age and comorbidity. In 26 episodes of RSE, after failure of first- and second-line drugs, 23 episodes were treated with a third-line drug that was non-anaesthetising in all but one case. In 12 of these episodes, seizures were controlled, but 11 patients needed further treatment [7] (class IV). These data indicate that the majority of patients with SE refractory to initial anticonvulsants was treated with further non-anaesthetising anticonvulsants which were successful in approximately half of the patients. However, these data did not differentiate between GCSE and NCSE.

The lowest class of evidence available is based on experts’ opinions. Two surveys have been performed, one on the treatment of GCSE amongst American neurologists [33] and another on the management of refractory GCSE and CPSE amongst epileptologists and critical care neurologists in Austria, Germany and Switzerland [34]. American neurologists did not agree on how to proceed in pharmacological treatment of SE after failure of benzodiazepines and phenytoin or fosphenytoin: more than 80% would not directly proceed to an anaesthetic (43% administer phenobarbital and 16% valproic acid), whilst 19% would directly administer anaesthetic [33] (class IV). However, this survey did not include the management of refractory CPSE. The European survey revealed that after failure of benzodiazepines and phenytoin two-thirds of the participants would administer in GCSE as well as in CPSE another non-anaesthetising anticonvulsant, the majority of participants preferred phenobarbital. Immediate administration of an anaesthetic was preferred by 35% in GCSE and by 16% in CPSE [34] (class IV). Three-fourths of the experts did not administer anaesthetics in refractory CPSE at all, whilst all did at some time point in GCSE. Administration of anaesthetics was withheld in CPSE: more than 60% of the participants administer
anaesthetics not earlier than 60 min after onset of status compared to only 21% of participants waiting that long in GCSE.

**Further non-anaesthetising anticonvulsants**

Though phenobarbital has been assessed in the initial anticonvulsive treatment [6] of SE, sufficient data on the efficiency of the substance after failure of benzodiazepines and phenytoin/fosphenytoin are missing. Doses of 20 mg/kg infused at a rate of 30–50 mg/min are used.

The role of i.v. valproic acid in the treatment of SE is yet to be defined. Valproic acid is a non-sedating substance that has not caused hypotension or respiratory suppression and has been reported to be effective in generalised convulsive and NCSE [35] (class IV). In a retrospective study that included 63 patients, efficacy rates of 63% and favourable tolerance of rapid administration ranging from 200 to 500 mg/min were reported [36] (class IV). Loading doses of 25–45 mg/kg [37] (class IV) and infusion rates up to 6 mg/kg/min have been suggested [38] (class IV). However, at present, there is inadequate data to justify its use before phenytoin.

**Anaesthetising anticonvulsants**

Most authorities recommend administering anaesthetic agents to a depth of anaesthesia which produces a burst suppression pattern in the EEG [34] (class IV) or an isoelectric EEG [39]. Studies are needed in this area, as these issues give rise to ethically highly problematic decisions.

Barbiturates, midazolam and propofol are commonly used in refractory SE [34] (class IV). There have been no RCTs comparing these treatment options. A systematic review of drug therapy for refractory SE including barbiturates, midazolam and propofol assessed data on 193 patients from 28 retrospective trials in an attempt to clarify this issue [40] (class IV). Pentobarbital was more effective than either propofol or midazolam in preventing breakthrough seizures (12 vs. 42%). However, in most studies barbiturates were titrated against an EEG burst suppression pattern whilst midazolam and propofol were administered to obtain EEG seizure cessation. Accordingly, side effects such as arterial hypotension were significantly more frequently seen with pentobarbital compared to midazolam and propofol (77 vs. 34%). Overall mortality was 48% but there was no association between drug selection and the risk of death.

**Recommendations**

**General initial management**

General management approaches in generalised convulsive, complex partial and subtle SE should include: assessment and control of the airways and of ventilation, arterial blood gas monitoring to see if there is metabolic acidosis and hypoxia requiring immediate treatment through airway management and supplemental oxygen, ECG and blood pressure monitoring. Other measures include i.v. glucose and thiamine as required, emergency measurement of antiepileptic drug levels, electrolytes and magnesium, a full haematological screen, and measures of hepatic and renal function. The cause of the status should be identified urgently and may require treatment in its own right (GPP).

**Initial pharmacological treatment of GCSE and NCSE**

The initial therapy of NCSE depends on the type and the cause. Subtle SE evolving from GCSE is refractory by nature and its further treatment is described below. Complex partial SE should be treated initially as GCSE. The preferred treatment pathway is i.v. administration of 4 mg of lorazepam, this dose is repeated if seizures continue for more than 10 min after first injection. If necessary, additional phenytoin (15–18 mg/kg) or equivalent fosphenytoin is recommended. Alternatively, 10 mg of diazepam directly followed by 15–18 mg/kg of phenytoin or equivalent fosphenytoin can be given, if seizures continue for more than 10 min after injection another 10 mg of diazepam is recommended. If necessary, additional lorazepam (4–8 mg) should be administered (Level A rating).

**General management of refractory status epilepticus**

GCSE that does not respond to initial anticonvulsant substances needs to be treated on an intensive care unit (GPP).

**Pharmacological treatment for refractory GCSE and subtle status epilepticus**

In GCSE and subtle SE we suggest to proceed immediately to the infusion of anaesthetic doses of midazolam, propofol or barbiturates because of the increasing risk of brain and systemic damage. Due to poor evidence we cannot recommend which of the anaesthetic substances should be administered first. We recommend the titration of the anaesthetic against an EEG burst suppression pattern. This goal should be maintained for at least 24 h. Simultaneously, antiepileptic the chronic medication the patient will be treated with in future should be initiated (GPP).

**Barbiturates:** To start with thiopental is administered as a 100–200 mg of bolus over 20 s then further 50 mg of boluses every 2–3 min until seizures are controlled, infusion 3–5 mg/kg/h. Pentobarbital (the first metabolite of thiopental) is marketed in the USA as the alternative to thiopental and is given as a bolus dose of
10–20 mg/kg followed by an infusion of 0.5–1 mg/kg/h increasing to 1–3 mg/kg/h.

**Midazolam:** Effective initial i.v. doses of midazolam are a 0.2 mg/kg bolus, followed by continuous infusion at rates of 0.1–0.4 mg/kg/h.

**Propofol:** Bolus (i.v.) of 2 mg/kg is administered followed by a continuous infusion of 5–10 mg/kg/h.

In cases of elderly patients in whom intubation and artificial ventilation would not be justified, non-anaesthetising anticonvulsants may be tried (see below) (GPP).

**Pharmacological treatment for refractory NCSE**

In complex partial SE, the time that has elapsed until termination of status is less critical compared to GCSE. Thus, general anaesthesia due to its possible severe complications should be postponed and non-anaestheticising anticonvulsants may be tried initially (GPP).

**Phenobarbital:** 20 mg/kg i.v., administration of additional boluses requires intensive care conditions.

**Valproic acid:** i.v. bolus of 25–45 mg/kg is administered followed by maximum rates up to 6 mg/kg/min.

If the treatment regimen includes the administration of anaesthetics then the same protocol applies as described for refractory GCSE.

**Update**

These guidelines will be updated when necessary and in any case in not more than 3 years.

**Conflicts of interest**

None declared.

**References**


32. Kaplan PW. No, some types of nonconvulsive status epilepticus cause little permanent neurologic sequelae (or: “the cure may be worse than the disease”). *Neurophysiologie Clinique* 2000; 30: 377–382.


