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Clinical trials in acute repetitive seizures and status epilepticus*

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ABSTRACT – This paper reviews the clinical trials in acute repetitive seizures and in tonic-clonic status epilepticus. There are good randomised controlled studies on the use of benzodiazepines in early status epilepticus, but an inadequate trial base in the later stages. Therapy has therefore to be based on open studies, although in the later stages there is also a dearth of open data. Tonic-clonic status epilepticus is a medical emergency and a condition with a significant mortality. The lack of information compromises optimal therapy. This paper reviews the reasons for the lack of data and the problems associated with collecting data. It is proposed that, in the first instance, the best way of improving the quality of evidence would be a multinational case registry of existing practice.

Key words: clinical trial, repetitive seizure, tonic-clonic, status epilepticus

Tonic-clonic status epilepticus (SE) is a serious condition with a significant mortality and is a medical emergency. The initial treatment is aimed at stopping seizures in order largely to avoid cerebral damage and other morbidity. All contemporary protocols take a staged approach to treatment (*figure 1*). Typically, in Stage 1 (the stage of early SE), therapy is with benzodiazepines. If seizures continue despite this therapy, the patient is said to be in Stage 2 (the stage of established SE) and therapy is with intravenous (IV) antiepileptic drugs such as phenytoin, phenobarbital, levetiracetam, or valproate. If seizures continue despite this treatment for up to two hours, the patient is said to be in Stage 3 (the stage of refractory SE) and general anaesthesia is usually recommended, at a dose which results in EEG burst suppression (a level of anaesthesia at which all seizure activity is usually controlled). A protocol such as this (albeit with variations) has been

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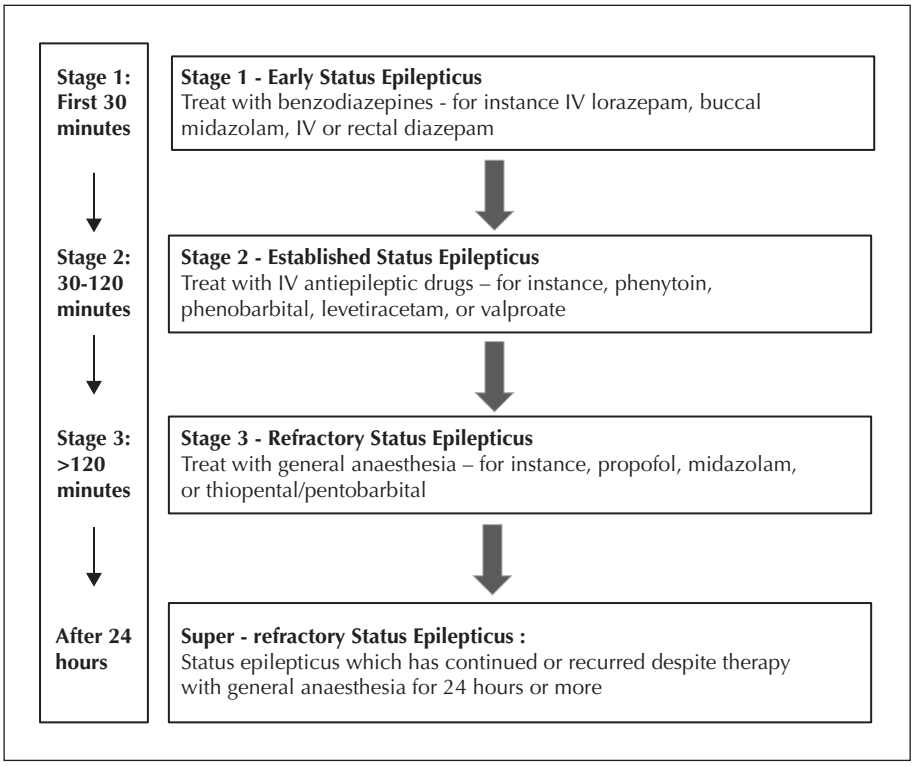

Figure 1. Flowchart showing the conventional three stages of therapy in convulsive SE, and the fourth stage (that of super-refractory SE) which is entered if none of the first three stages are effective (from Shorvon and Ferlisi [2011]).

recommended on numerous occasions in the past three decades (examples include: Delgado-Escueta *et al*., 1983; EFA Working Group, 1993; Shorvon, 1994; Appleton *et al*., 2000; Meierkord *et al*., 2006; Minicucci *et al*., 2006; Shorvon *et al*., 2008; Meierkord *et al*., 2010). Recently, super-refractory SE has been introduced as a term for those patients whose seizures continue despite initial anaesthesia.

These protocols are, however, derived from a generally very poor evidential base, and there is a dearth of high quality clinical trials in this area. In this paper, the current evidence base relating to clinical trials will be reviewed, some problems of conducting clinical trials in this area discussed, and suggestions made for improving this evidence base.

This paper will be concerned with (a) acute therapy after a convulsive seizure, including single seizures and acute repetitive seizures (clusters of seizures and serial seizures) and (b) therapy of SE. Only tonic-clonic (convulsive) seizures will be considered here and not other forms of epilepsy, for which the problems are quite different.

Clinical trials of acute therapy after a single seizure, acute repetitive seizures (including serial seizures and seizure clusters), and prophylactic therapy

Single seizures

It is generally accepted that short-lived tonic-clonic seizures do not require emergency drug treatment. This is because the seizures are usually self-limiting and will anyway have stopped before any drugs, even if administered as an emergency, will have had a chance to take effect. Only in the following circumstances should antiepileptic drug therapy be considered: convulsive movements continue for longer than 5-10 minutes, or longer than is customary for the individual patient; consciousness is not rapidly recovered; seizures rapidly recur; and the cardio-respiratory system is impaired. In these eventualities, emergency therapy should be considered. There are no controlled or comparative studies in this area.

Serial seizures and seizures occurring in clusters

In some patients, serial seizures or clustering of seizures regularly occur. The clustering may be time-locked to a provocation, such as menstruation. Acute therapy after the first seizure (or early in a cluster/series) can be given in an attempt to prevent subsequent attacks. Clusters can occur with drug withdrawal (for instance in an epilepsy monitoring unit; Rose *et al*., 2003) and the restitution of the withdrawn drug will usually terminate the seizure cluster.

The standard therapy is with a benzodiazepine. There are a number of open studies and series, and a few comparative trials of benzodiazepines used for acute repetitive seizures (in addition to the studies of early SE which are discussed below). Cereghino *et al*. (1998, 2002) and Dreifuss *et al*. (1998) compared rectal diazepam gel with placebo in children and adults. In one study of 96 adults in a double-blind, placebo-controlled trial, rectal diazepam was found to be more effective than placebo, with a 71% 12-hour seizure control rate with rectal diazepam compared to 28% with placebo, a longer time to next seizure with rectal diazepam and a reduction in the median number of seizures (Cereghino *et al*., 2002). A similar study, with similar results, was conducted in children (Kriel *et al*., 1999). Rectal lorazepam has been compared to diazepam in an open comparative study (Appleton *et al*., 1995). Other non-benzodiazepine drugs have also been studied in comparative trials, but none in a blinded fashion. These include the study of Gilad *et al*. (2008), comparing 74 adult patients treated with either valproate or IV phenytoin in a consecutive open study with equally good results (88% seizure cessation in both groups). Other largely open studies of phenytoin (Wallis *et al*., 1968), levetiracetam (Goraya *et al*., 2008), valproate (Limdi and Faught, 2000) and paraldehyde (Rowland, 2009) have been carried out.

Where oral therapy is sufficient, in serial seizures or a cluster of seizures, clobazam (10-20 mg) is the usual choice in Europe. An oral dose of clobazam will take effect within 30 minutes or so and last for 12-24 hours. There are no controlled or comparative studies of this indication despite its widespread use.

Intermittent prophylactic treatment

In a minority of patients, the timing of seizure occurrence is predictable, for instance, in relation to menstruation (catamenial epilepsy). Occasionally, in such patients, intermittent therapy with either clobazam (10-20 mg/day) or acetazolamide (250-500 mg/day) can be given for a few days to cover the risky period. A single double-blind, cross-over trial of oral clobazam, compared to placebo, in catamenial epilepsy was reported, showing clobazam to be superior (Feely *et al*., 1982). Clobazam has the advantage that it causes much less sedation than either diazepam or lorazepam.

A single dose of clobazam (10 mg) can also be taken in situations where seizures would be particularly hazardous (for instance on the day of travel or examinations) or in susceptible individuals at times when seizures are particularly likely to occur (*e.g*. after sleep deprivation, alcohol, labour or delivery, etc.). The use of occasional intermittent clobazam in these settings, as a "booster" to conventional therapy, can be highly effective and is an under-used resource in my experience. However, there are no comparative trials of the use of clobazam in this way.

Clinical trials of IV therapy in the early stage of SE

The early stage of SE is usually treated in a similar way to that of seizure clusters. The difference is simply a matter of degree of severity and of timing (SE traditionally is defined as a seizure continuing for 30 minutes or more, although recent definitions have suggested shortening this period to five minutes which further blurs the distinction between an acute seizure and SE). Thus, some studies refer to therapy for acute seizures and some for SE. The usual therapy is with a benzodiazepine, and there are a number of well-conducted RCTs of benzodiazepine therapy at this stage of SE.

Leppik *et al*. (1983) were the first to compare lorazepam and diazepam for the treatment of SE in a double-blind, randomised trial. Seventy-eight patients with 81 episodes were enrolled. Patients received one or two doses of either 4 mg of lorazepam or 10 mg of diazepam, intravenously. Seizure control was achieved in 89% of the episodes treated with lorazepam and in 76% treated with diazepam. The times for onset of action of the medications did not differ significantly. Another influential study is that of the Veteran Affairs Status Epilepticus Cooperative Study Group (Treiman *et al*., 1998) in which four IV treatment regimens were compared as initial treatment in convulsive SE: diazepam followed by phenytoin, lorazepam, phenobarbital, and phenytoin. A total of 384 patients were studied and lorazepam was successful in 64.9%, phenobarbital in 58.2%, diazepam plus phenytoin in 55.8% and phenytoin in 43.6%. Lorazepam was significantly superior to phenytoin in a pairwise comparison, but no other significant differences were found.

A classic study at this stage of SE (or acute seizures) was that of Alldredge *et al*. (2001) comparing IV lorazepam (2 mg), diazepam (5 mg), and placebo. Of the 205 patients enrolled, 66 received lorazepam, 68 received diazepam, and 71 received placebo. SE had been terminated in significantly more patients treated with lorazepam (59%) or diazepam (43%) than in patients

given placebo (21%). The odds ratio for termination of SE by lorazepam compared to placebo was 4.8 (95% CI: 1.9 to 13.0), 1.9 (95% CI: 0.8 to 4.4) for lorazepam compared to diazepam, and 2.3 (95% CI: 1.0 to 5.9) for diazepam compared to placebo. It was concluded that benzodiazepine was better than placebo and there was a trend towards the superiority of lorazepam over placebo. Of course, the dose may be important; 5 mg diazepam is a rather low dose and higher doses may have been more efficacious. Sreenath *et al*. (2010) recently compared lorazepam with diazepam/phenytoin as first line treatment of SE in a randomised trial in 178 children and found no difference in efficacy (with, remarkably, both treatments controlling status in 100% of cases). Qureshi *et al*. (2002) also compared IV lorazepam and diazepam as first-line therapy in 85 children with prolonged seizures. This was achieved in two periods; in the first six months diazepam was used and in the second six months lorazepam. The seizures were controlled in 65% patients treated with diazepam (median time of three minutes) and in 65% of patients treated with lorazepam (median time of five minutes).

Clinical trials of non-IV therapy ("out of hospital"): therapy of acute seizures and early SE

In recent years, the distinction between "in-hospital" and "out-of-hospital" treatment has been stressed. This is a useful distinction, for out-of-hospital therapy (*i.e*. therapy in the community) often requires non-IV treatment to avoid the risk of acute cardio-respiratory collapse. In a hospital setting, IV therapy is practical and the presence of resuscitation facilities allows therapy to be given even if there is a risk (albeit small) of cardio-respiratory collapse. Out-of-hospital treatment is also useful in locations where emergency hospital facilities may be scarce or difficult to reach, and so there are several well-conducted controlled studies from developing countries and rural areas.

The recent emphasis has been on the use of midazolam as a buccal, intramuscular (IM) or intranasal (IN) preparation. Midazolam is the benzodiazepine chosen as it is the only water soluble benzodiazepine and thus is absorbed quickly by these non-IV methods of administration.

The classic study of buccal midazolam was that of Scott *et al*. (1999). In this study, conducted at a residential school with on-site medical facilities, 42 young people with severe epilepsy were enrolled in advance. Continuous seizures of more than five minutes duration were randomly treated with buccal midazolam (40 seizures in 14 patients) or rectal diazepam (39 seizures in 14 patients). Seizures ceased with midazolam in 30 (75%) and diazepam in 23 (59%) and both controlled seizures within minutes of the administration of the benzodiazepines. It was concluded that buccal midazolam was at least as effective as rectal diazepam and that administration via the mouth is more socially acceptable and convenient. The definitive study was that of McIntyre *et al*. (2005). This was a multicentre, randomised, controlled trial comparing buccal midazolam with rectal diazepam in 219 separate episodes in 177 children (median age of three years). Seizures were controlled in 56% (61 of 109 episodes) with buccal midazolam and 27% (30 of 110 episodes) with rectal diazepam (percentage difference 29%, 95% CI: 16-41). It was concluded in this study that buccal midazolam was more effective than rectal diazepam for children presenting to hospital with acute seizures. Since then, several other comparative studies, some from developing countries, have been carried out demonstrating the effectiveness of buccal midazolam. In India, Talukdar and Chakrabarty (2009) compared buccal midazolam and IV diazepam in 128 children. The frequency of overall control of convulsive episodes within five minutes was 85% and 93.3% in buccal midazolam and IV diazepam groups, respectively. The mean time to control was less for IV diazepam, although the time taken to prepare and administer the IV injection resulted in a longer time from onset of seizure to control in the diazepam group. In Uganda, Mpimbaza *et al*. (2008a) reported a single-blind, randomised study comparing buccal midazolam with rectal diazepam in 330 children (aged 3 months to 12 years). Treatment failures occurred in 71 (43.0%) of 165 patients who received rectal diazepam compared to 50 (30.3%) of 165 patients who received buccal midazolam; buccal midazolam was considered more effective and as safe as rectal diazepam. The control rates were lower in those with acute malaria which was the commonest aetiology of the seizures. In Norway, Nakken and Lossius (2011) compared rectal diazepam and buccal midazolam in adults in a residential epilepsy centre in an unblended sequential fashion. Convulsive SE was terminated significantly faster with buccal midazolam (2.8 minutes) than with rectal diazepam (5.0 minutes). There was no significant difference in the proportion of patients whose seizures were controlled with diazepam (83.3%) and midazolam (74.4%). Both treatment options were well tolerated, but all of the nursing staff and patients preferred the buccal route of administration.

Other routes of administration have also been studied. Chamberlain *et al*. (1997) compared IM midazolam with IV diazepam in an open study of 24 patients (13 midazolam, 11 diazepam). One patient in each group failed therapy but patients in the midazolam group received medication sooner (3.3±2.0 *vs* 7.8±3.2 minutes) and had more rapid cessation of their seizures (7.8±4.1 *vs* 11.2±3.6) than patients randomised to

receive diazepam. The authors concluded that IM midazolam was an effective anticonvulsant for children, resulted in more rapid cessation of seizures because of more rapid administration, and that the IM route of administration may be particularly useful in the pre-hospital setting. The recently published RAMPART study was a definitive multicentre, double-blind, randomised, non-inferiority trial comparing IM midazolam (448 subjects) with IV lorazepam (445 subjects), given by paramedics for convulsions lasting more than five minutes (Silbergleit *et al*., 2011, 2012). A network (Neurological Emergency Treatment Trial; NETT) was used to recruit and the recruitment rate was considerably faster than planned (which must be almost unique to clinical trials). There were 17 hubs and 112 spoke sites (EMS agencies and regional hospitals). The treatment was administered by paramedics (4,000 were trained) and the study sites spanned the whole of the USA. The success of the study undoubtedly depended on the quality of the leadership of the trial and the network design. There was a double-dummy design and the primary outcome measure was absence of seizures at the time of arrival at the emergency room, which was 73.4% for the IM midazolam and 63.4% for the IV lorazepam patients (not a significant difference). The time from the start of therapy to the end of the seizure was not substantially different between either group, nor were side-effects. The authors concluded that IM midazolam was at least as safe and effective as IV lorazepam as out-of-hospital therapy (Silbergleit *et al*., 2012).

An alternative method of administration of midazolam in the out-of-hospital setting is the intranasal route. Scheepers *et al*. (2000) reported, and have remained enthusiastic about, the first open, non-comparative study of this route of administration. Twenty-two patients received 84 treatment episodes and 79 of these were considered clinically effective. Fisgin *et al*. (2002) published a comparative study of rectal diazepam and IN midazolam carried out in Turkey. The seizures in 13 (60%) children given diazepam and 20 (87%) children given midazolam were controlled within 10 minutes. It was concluded that IN midazolam was more effective than rectal diazepam. Mahmoudian and Zadeh (2004) in Iran then reported a study of 70 children aged 2 months to 15 years. IN midazolam at 0.2 mg/kg was compared to IV diazepam at 0.2 mg/kg. Both were equally effective. The mean time to control of seizures was slightly slower (3.58 minutes; SD: 1.68) with midazolam than with diazepam (2.94 minutes; SD: 2.62), but this did not take into account the time required to insert the IV line. In the US, a recently reported prospective, randomised, comparative study compared IN midazolam with rectal diazepam in 358 children after an acute seizure, and no differences were found between the two groups, although IN midazolam scored higher for ease of administration and overall satisfaction (Holsti *et al*., 2010).

Clinical trials in the stage of established Status Epilepticus

The standard therapy at this stage of SE is either IV phenytoin (often given with diazepam) or IV phenobarbital. There are a number of open case series, but a surprisingly small number of comparative studies in this area, and only three RCTs.

Indeed, there are only six published studies (excluding abstracts) of a total of 595 adults and children with various forms of SE with phenytoin therapy. Some were not pre-treated with benzodiazepines and doses varied. The overall success rate with IV phenytoin ranged from 42% in the randomised controlled study (in two studies where patients were not tried first with benzodiazepine therapy (Treiman *et al*., 1998; Misra *et al*., 2006) to 100% (mean response rate of 70%). There is an even smaller evidence base for phenobarbital. Shaner *et al*. (1988) published a randomised, non-blinded, comparative trial of 36 consecutive patients with generalised convulsive SE who were treated with either a combination of diazepam and phenytoin or phenobarbital. They found that the cumulative convulsion time (total time spent in active convulsive movements) was shorter for the phenobarbital group than for the diazepam/phenytoin group (median of five *vs* nine minutes) and time from initiation of therapy to the end of the last convulsion was also shorter for the phenobarbital group (median of 5.5 *vs* 15 minutes). They concluded that phenobarbital was the therapy of choice. Agarwal *et al*. (2007) compared phenytoin and valproate in benzodiazepine-resistant patients. A total of 100 age and sex-matched patients were randomly divided into a group of 50 patients treated with IV valproate and 50 patients treated with IV phenytoin. Valproate controlled seizures in 88% and phenytoin in 84%. Valproate was found to be easier to administer and better tolerated.

Fosphenytoin is frequently recommended as an alternative to phenytoin in this stage of SE and is licensed for this use. However, there are no controlled studies of its effectiveness in SE and its license was granted largely on the basis that it is a prodrug of phenytoin, as a standard therapy, with pharmacokinetic bioequivalence. It is not widely used in Europe.

Other drugs are widely used at this stage of SE, notably valproate, levetiracetam, and, increasingly, lacosamide. There are three reported randomised comparative trials of the use of valproate, each from India. Misra *et al*. (2006) compared valproate to phenytoin as first line therapy. The study was underpowered and the use of a one-tailed test has been criticised

(Trinka, 2009). Mehta *et al*. (2007) compared IV diazepam and phenytoin in 40 children unresponsive to earlier therapy. Non-responders were then randomised to IV valproate or diazepam infusion with no clear difference in efficacy, but valproate was safer. The third study comparing valproate with phenytoin is mentioned above (Agarwal *et al*., 2007). The total number of patients in all studies, including open case series and case reports amounts to about only 800. For lacosamide and levetiracetam, there are no randomised controlled studies, and the total number of patients included in the studies of these drugs for SE (in Stage 1 or 2, and not necessarily in benzodiazepine-resistant patients) is: for lacosamide, 126 patients in two studies (Kellinghaus *et al*., 2011) and for levetiracetam, 1,033 patients in 34 studies (of which only seven were prospective). This is a wholly unsatisfactory situation.

Clinical trials in the stage of refractory SE and super-refractory SE

In SE which has not responded to either first stage therapy (benzodiazepine) or second stage therapy (phenytoin, phenobarbital, valproate and levetiracetam), it is usually recommended that therapy with general anaesthesia is initiated. This is the stage of refractory SE. The anaesthetics most commonly used are thiopental, midazolam, and propofol. There are no comparative trials comparing these regimens, despite the fact that refractory SE is a serious condition with a mortality rate of over 35% (Shorvon and Ferlisi, 2012). A randomised, single-blind, multicentre trial has been attempted with adults with refractory SE not due to cerebral anoxia, comparing propofol and barbiturate therapy; 150 patients were required to obtain sufficient power, but after three years only 23 patients were recruited (Rossetti *et al*., 2011).

There is an extensive literature review of studies in this area (Shorvon and Ferlisi, 2011; Shorvon and Ferlisi, 2012). Outcome was recorded for 920 patients receiving one of the three common anaesthetic drugs (192 patients treated with pentobarbital/thiopental, 143 with propofol, and 585 with midazolam; although a single, rather briefly documented study [Hayashi *et al*., 2007] contributed 306 [52%] of the midazolam cases). These were largely anecdotal reports from open case series (often retrospective) or case reports, and in this situation, none of the drugs can be compared to one another. Furthermore, as it was pointed out, a number of significant potential biases exist. Propofol and midazolam were more recently introduced than the barbiturate anaesthetics which have been in usage for this indication for well over 50 years, and so the barbiturate outcomes were reported largely at a time when ITU practice was not as well developed as it is now (about two thirds of cases between 1980-1999, compared to <10% of propofol and midazolam cases). The most severe cases, and those with certain severe aetiologies (*e.g*. hypoxia), are more likely to be treated with barbiturate, and cases which are unresponsive to midazolam or propofol are nowadays likely to progress to barbiturate therapy. Different treatments are preferred at different ages, for instance, children are least likely to be treated with propofol.

In these studies, patients of all ages and with a range of aetiologies were included. The median duration of therapy was 53 hours (range: 11-1,200) with thiopental/pentobarbital, 32 hours (range 0.5-432) with propofol, and 16 hours (range 10-240) with midazolam, perhaps reflecting the greater severity of the barbiturate cases. All drugs caused complications, most commonly hypotension and respiratory depression which can be severe. The infusion doses also varied considerably from report to report, ranging from 0.5-20 mg/kg/h for thiopental/pentobarbital, 0.1-24 mg/kg/h for propofol, and 0.02-1.8 mg/kg/h for midazolam. The rates of control and failure of control are shown in *table 1*.

Table 1. Overall outcome of anaesthetic therapy.

	Thiopental/ pentobarbital (*n*=192)	**Midazolam (*n*=585)**	**Propofol (*n*=143)**
Control (%)	64	78	68
No control ever achieved* (%)	5	16	11
Breakthrough seizures (%)	0	3	1
Withdrawal seizures (%)	9	<1	6
Therapy failure because of side-effects (%)	3	<1	6
Death during therapy (%)	19	2	8

* Excluding those who died without control who are included in the "death during therapy" category, and those who switched because of side effects who are included in the "Therapy failure because of side-effects" category (from Shorvon and Ferlisi, 2012).

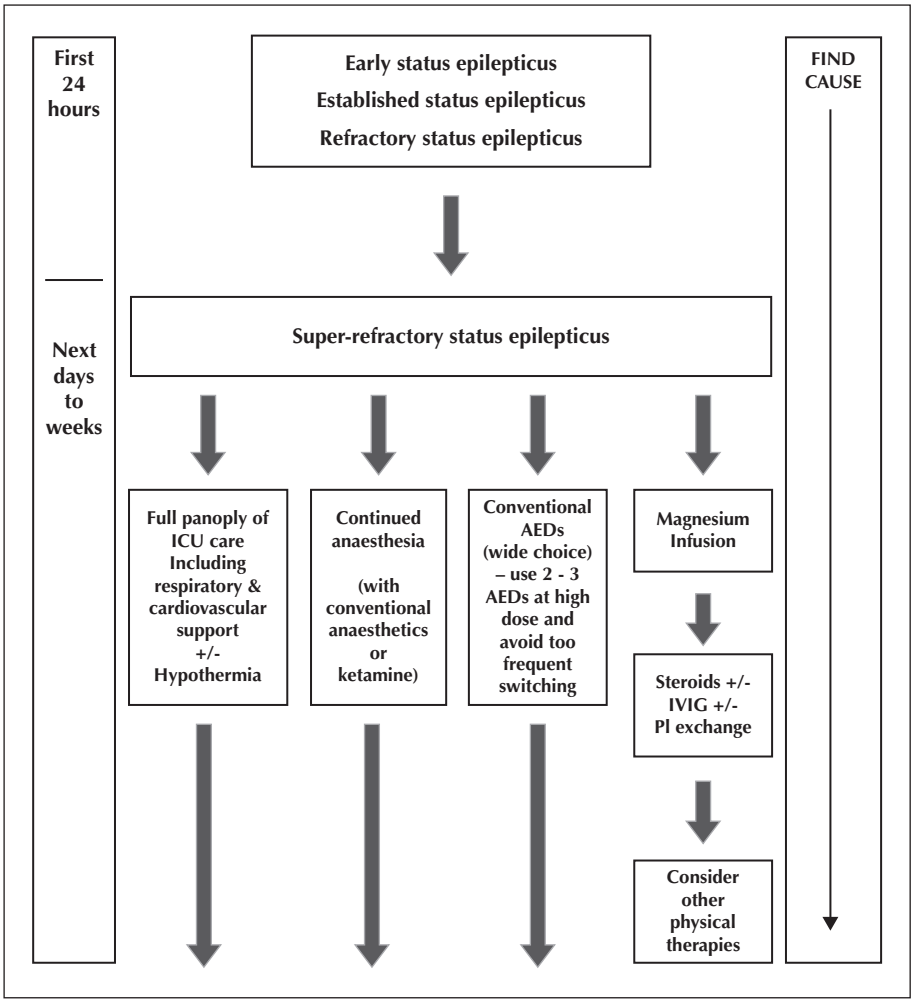

Figure 2. Flowchart showing the therapeutic approach employed in the phase of super-refractory SE (from Shorvon [2011]).

Other treatments for the stage of super-refractory SE were even less well studied, even when widely used. A proposed flowchart for the therapy of super-refractory SE is shown in *figure 2* and the range of treatments, the number of reports in which outcome is reported, and the number of patients from this literature review are presented in *table* 2.

There were a number of factors, clear from this literature review, that make a robust assessment of the value of these therapies difficult, if not impossible (Shorvon and Ferlisi, 2011; Shorvon and Ferlisi, 2012):

– the lack of randomised or controlled studies (see above);

– the small number of individuals treated. Many of the therapies, even those very widely used in routine practice, are based on an extremely small number of published cases;

– co-medication and changing doses of co-medication. Therapies in the super-refractory period of status are almost always given in combinations, and assessment of a therapy is often complicated by concurrent changes in dosages, or physical parameters;

– delay in responses. Reports of responsiveness for some therapy include patients who responded days or weeks after the initial application of treatment;

– some therapies are widely used and yet the published literature is extremely small. Where this is the case, the small number is likely to represent very considerable publication bias.

Conclusions and the future

In this paper, the evidence base for therapy in acute repetitive seizures and in SE is reviewed. In my view, there are sufficient studies to draw robust conclusions from the stage of early SE and for acute repetitive seizures (but not for prophylactic therapy). The use of benzodiazepines seems well supported by the

Table 2. The published literature on treatment outcomes.

Therapy	Number of published papers reporting outcome data	Number of published cases in which outcome data is provided
Pentobarbital/ thiopental	23	192
Propofol	24	143
Midazolam	20	585
Ketamine	7	17
Inhalational anaesthetics	7	27
Hypothermia	4	9
Magnesium	2	3
Pyridoxine	2	2
Immunotherapy	8	21
Ketogenic diet	4	14
Vagal nerve stimulation	4	4
Deep brain stimulation	1	1
ECT	6	8
Emergency neurosurgery	15	36
CSF drainage	1	2
Topiramate	8	24
Levetiracetam	8	35
Lacosamide	2	10

Note: All patients had received more than one therapy, but we have included in this table only the therapies highlighted in individual papers (from Shorvon and Ferlisi, 2012).

evidence, although there is little clear evidence of any difference in efficacy (at least short-term efficacy) between difference compounds. Other drugs are less well studied. Another new approach is to initiate therapy at the earliest stage with benzodiazepine and other therapies combined, in view of the seizure-induced rapid reduction of GABAergic and increase in glutaminergic receptors on cell membranes and the resulting seizure-induced resistance to GABAergic drugs. In an experimental model, this "rational polytherapy" approach (using diazepam, ketamine and valproate or benzodiazepine with ketamine and brivaracetam, compared to diazepam alone) seemed more efficacious and less toxic than benzodiazepines alone (Wasterlain *et al*., 2011).

In contrast to the reasonable evidence base in early status, that for the stage of established SE is very limited. There are a handful of randomised controlled studies and those that exist are underpowered. The number of patients in open studies is also small and the quality of the studies generally poor. Currently, there is a proposal for a new study with funding agencies, the Established Status Epilepticus Treatment Trial (ESETT), and this should provide high quality evidence in this field where this is greatly needed. The design of this study has brought up significant issues which need to be addressed by any study in this area (Cock, 2011). This study aims to compare levetiracetam, valproate, and fosphenytoin in patients with benzodiazepine-resistant SE. The primary outcome is control of SE at two hours after infusion. It will have an adaptive trial design and a sample size of 1,720 subjects, which can be reduced to 1,100 in an adaptive design, which is the minimum number required to detect a 10% difference at a power of 80% and a significance level of 5%. There has been much debate about the need for consent, blinding, the role of EEG, and the secondary endpoints. Blinding the study results in a complex logistical design with the need for dummy infusions of various speeds. Another surprising problem has been the poverty of evidence for the effectiveness of the standard therapy (phenytoin) which is necessary to make the power calculations (in the end, an estimate of 50% responsiveness was made). The study has to be multinational to meet recruitment targets and will take place in the US and Europe. The same network as for the RAMPART study will be used in the US. If six patients are recruited annually from 50 centres, it is assumed that the study will need four years to complete. The planning and grant application phase has already taken four years due to the large logistical and regulatory difficulties in conducting such studies. The delay has other consequences. Lacosamide is a therapy which currently has no equipoise and so cannot be included as an arm of the study, but by the time the study is completed, may well be in wide use. The built-in obsolescence of a study such as this is exacerbated by the logistical and regulatory difficulties. Also, the cost becomes extremely high and over 20 million US dollars is the current estimate. The cost and the delay, induced by the logistical and regulatory difficulties, are to the detriment of the many patients in the interim who will fail to receive optimal therapy. It is worth noting, also, that this is an area in which there are no industry-sponsored studies, reflecting the problems that the current regulatory environment creates, and any study proposed has to be academically-initiated.

Finally, there are no controlled or randomised studies at the stage of refractory or super-refractory SE. Indeed, the therapies in wide use are often based on an extraordinarily small number of reported cases. There are many problems with studies in this area (some listed above) and there is little hope of a satisfactory controlled or randomised study being performed for any of the therapies. Because of this, it is proposed that the best way of improving the quality of evidence, at least in the first instance, would be a European wide registry, collecting data on existing practice. Such a registry is currently being planned. □

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