The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy

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In a previous paper, we reviewed the range of therapies available for the treatment of super-refractory status epilepticus. Here we report a review of the outcome of therapies in refractory and super-refractory status epilepticus. Patients (n = 1168) are reported who had therapy with: thiopental, pentobarbital, midazolam, propofol, ketamine, inhalational anaesthetics (isoflurane, desflurane), antiepileptic drugs (topiramate, lacosamide, pregabalin, levetiracetam), hypothermia, magnesium, pyridoxine, immunotherapy, ketogenic diet, emergency neurosurgery, electroconvulsive therapy, cerebrospinal fluid drainage, vagal nerve stimulation and deep brain stimulation. The outcome parameters reported include control of status epilepticus, relapse on withdrawal, breakthrough seizures and mortality. Where reported (596 cases), the long-term outcome was found to be death (35%), severe neurological deficit (13%), mild neurological deficit (13%), undefined deficit (4%) and recovery to baseline (35%). The quality of reported outcome data is generally poor and the number of cases reported for all non-anaesthetic therapies is low. Outcome assessment is complicated by changes in co-medication, delay in response and publication bias. Given these deficits, only broad recommendations can be made regarding optimal therapy. An approach to therapy, divided into first-line, second-line and third-line therapy, is suggested on the basis of this outcome evaluation. The importance of treatments directed at the cause of the status epilepticus, and of supportive ITU care is also emphasized.

Keywords: status epilepticus; outcome; refractory epilepsy; morbidity; mortality; therapy

Abbreviations: ITU = intensive treatment unit

Introduction

The treatment of the earlier phases of tonic–clonic status epilepticus has been well studied and discussed in recent years. There are a number of similar guidelines and protocols published, all of which include the initial use of benzodiazepines, followed by intravenous antiepileptic drugs such as phenytoin, phenobarbital or valproate, and then if necessary the induction of anaesthesia (examples include Delgado-Escueta et al., 1984; EFA Working Group 1993; Shorvon, 1994; Appleton et al., 2000; SIGN 2003; Kälviäinen et al., 2005; Meierkord et al., 2006, 2010; Minicucci et al., 2006; Holtkamp, 2006, 2007; Shorvon et al., 2008; Aranda et al., 2010; Rossetti, 2010; Rossetti and Lowenstein, 2011). This is a well-trodden path which, although based on an inadequate evidence base, is widely accepted and practiced.

In this article, we focus on the outcome of patients with refractory status epilepticus and super-refractory status epilepticus. Refractory status epilepticus is defined for the purposes of this article as ‘status...
epileptics requiring general anaesthesia’. Super-refractory status epilepticus is defined as ‘status epilepticus that continues 24 h or more after the onset of anaesthesia, including those cases in which the status epilepticus recurs on the reduction or withdrawal of anaesthesia’. Although constituting a minority of cases of status epilepticus (~10–15% of all those presenting to hospital in status epilepticus develop super-refractory status epilepticus; Novy and Rossetti, 2010), appropriate therapy of these cases is poorly studied.

The cases considered here are of convulsive status epilepticus and we have not included non-convulsive cases, except where these evolved from a convulsive stage. Anaesthesia is not often required in primarily non-convulsive cases, and certainly should not be given early, and the response to treatment in these cases may well differ. In this article, the publications reporting successful outcome of anaesthetic drugs do not always specify the time of anaesthesia, and so might possibly include some patients who have refractory not super-refractory status epilepticus (by the definitions used in this article). However, for all failures of anaesthetics (by definition), and for all the other therapies administered, the therapies were used at the stage of super-refractory status epilepticus.

A number of therapies are in current usage and the literature reporting these therapies has been reviewed in detail elsewhere (Shorvon and Ferlisi, 2011). The current review aims to accompany the previous paper and provide a synthesis, from this published literature from 1981, of the outcome of these therapies. The therapies considered include thiopental, pentobarbital, midazolam, propofol, ketamine, inhalational anaesthetics (isoflurane, desflurane), antiepileptic drugs (topiramate, lacosamide, pregabalin, levetiracetam), hypothermia, magnesium, pyridoxine, immunotherapy, ketogenic diet, emergency neurosurgery, electroconvulsive therapy (ECT), CSF drainage, vagal nerve stimulation and deep brain stimulation. Therapy with the following older drug therapies has also been reported but not in recent times, and these will not be considered further: chloral, bromide, paraldehyde, etomidate, lignocaine, and a variety of other barbiturate and benzodiazepines such as bromethol, hexobarbital, methohexital, butallylonal, seconobarbital, amylobarbitali, diethylamine barbiturate, nitraepam, clonazepam and clonazepam.

Method of assessing and categorizing outcome

Details of the literature used as the basis of this review are published elsewhere (Shorvon and Ferlisi, 2011, including the associated Supplementary material). Of these 159 papers, 121 published since 1981 reported outcome data in 1061 patients in sufficient detail. These papers form the evidence base of this review and are listed in Appendix 1. Details of the analysis of each paper are provided in the Supplementary material. We also analysed an additional 21 papers reporting outcome of 107 patients with super-refractory status epilepticus treated with antiepileptic drugs (topiramate, levetiracetam, pregabalin and lacosamide) making a total of 1168 patients studied. It is salutary to note that there is only one randomized or controlled study of any of these therapies (a trial comparing thiopental and propofol) requiring 150 patients for adequate power but which managed to recruit only 24 patients and therefore failed to reach any conclusions (Rossetti et al., 2011). Apart from this study, the evidence base consists entirely of single case reports or small series (Table 1).

Furthermore, none of the widely recommended drugs or procedures has been subjected to an adequate systematic review. There are a number of other papers, not considered here, where treatment (often with multiple therapies) is mentioned only in passing, and where there are insufficient data to provide any assessment of outcome. In papers where data on a particular therapy is focused upon, and other therapies are mentioned in passing, we have included only the therapy with sufficient data. We have considered only therapies aimed primarily at the control of seizures and not therapies used to treat the underlying cause of the status epilepticus (e.g. magnesium in magnesium deficiency, pyridoxine in pyridoxine-dependant patients or immunotherapy in identifiable immunological disease).

Outcome at the refractory and super-refractory stages of status epilepticus can be categorized into one of the following six categories (one successful category and five types of failure).

(i) Successful therapy: the status epilepticus is completely controlled by the therapy, without breakthrough or withdrawal seizures, or discontinuation due to side-effects, or death during the therapy.

(ii) Initial failure: the therapy failed to control status epilepticus at all.

(iii) Breakthrough seizures: recurrence of status epilepticus during the treatment, despite initial control, resulting in the need for a change of therapy (and does not include those cases in which seizures recurred and control was gained by increasing the dose—these cases are included in Category (i)).

(iv) Withdrawal seizures: recurrence of status epilepticus during or immediately after the tapering or withdrawal of the therapy.

### Table 1 The published literature on treatment outcomes

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Number of published papers reporting outcome data</th>
<th>Number of published cases in which outcome data are provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentobarbital/thiopental</td>
<td>23</td>
<td>192</td>
</tr>
<tr>
<td>Propofol</td>
<td>24</td>
<td>143</td>
</tr>
<tr>
<td>Midazolam</td>
<td>20</td>
<td>585</td>
</tr>
<tr>
<td>Ketamine</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Inhalational anaesthetics</td>
<td>7</td>
<td>27</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Magnesium</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td>Ketogenic diet</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Vagal nerve stimulation</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Deep brain stimulation</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ECT</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Emergency neurosurgery</td>
<td>15</td>
<td>36</td>
</tr>
<tr>
<td>CSF drainage</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Topiramate</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>8</td>
<td>35</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>

All patients had received more than one therapy, but we have included in this table only the therapies highlighted in individual papers. The anaesthetic reports include patients with refractory and super-refractory status epilepticus.
resulting in the need for a change of therapy (and does not include those in whom control was achieved by reintroducing the same drug).

(v) Intolerable side-effects: the therapy resulted in side-effects necessitating alternative therapy.

(vi) Death during the course of the treatment. Some of these deaths will be due to the underlying cause, but as it is often impossible to attribute mortality accurately, and as treatment may play a contributing role in the outcome of these cases, all such deaths are included in this category (note, deaths occurring after the therapy has been discontinued are not included).

Although we have applied this scheme to all cases, a number of differences between the types of therapy exist. All anaesthetic drugs, if used in high enough doses, will result in a depth of anaesthesia sufficient to abolish seizure activity. In this sense, any effective anaesthetic will inevitably initially control status epilepticus, provided a sufficient dose can be given. If initial failure does occur [Category (iii)], it will be usually because the appropriate dose cannot be reached because of side-effects (notably hypotension or cardio-respiratory depression). It is usual to attempt a dose of anaesthesia that produces the EEG pattern known as ‘burst suppression’, as at this level it is rare for any epileptic electrographic activity to be manifest, but often the dose required will cause side-effects and cannot be attained. In some reports though, it is possible that therapy was discontinued prematurely at too low a dose for other reasons. Other types of treatment are either given as continuing infusions, repeated dosing, or single one-off therapies. In these cases, the potential for failure of initial therapy is higher. For one-off therapies, the category of breakthrough seizures cannot apply, and Category (iv) (withdrawal seizures) is used to include cases in which seizures were initially controlled but rapidly returned after the cessation of the one-off therapy.

### Results

#### Anaesthetic treatments

These are the best documented of the available therapies. In total, we found outcome recorded for 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, as mentioned above, largely anecdotal reports and each drug cannot be compared with the others. Furthermore, a number of significant potential biases exist. Propofol and midazolam are more recently introduced than the barbiturate anaesthetics, which have been used in this indication for well over 50 years, and so the barbiturate outcomes were reported largely at a time when Intensive Treatment Unit (ITU) practice was not as well developed as now (about two-thirds of cases between 1980 and 1999, compared with <10% of propofol and midazolam cases); the most severe cases, and those with certain severe aetiologies, are more likely to be treated with barbiturates; cases that 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.

#### Control, failure of control and side-effects

We found control of refractory and super-refractory status epilepticus in 74% (678/920) of the reported cases (Table 2). The rate of initial control on barbiturate was 64%, midazolam 78% and propofol 68%. As mentioned above, an anaesthetic drug will inevitably control status epilepticus provided the dosage is high enough, and the failure to gain control is usually due to either too low a target dose or dose limitation caused by side-effects. Side-effects (usually hypotension or cardio-respiratory depression) were reported to require a change in therapy in 3% of patients on barbiturates, and 6% on propofol, usually isolated symptoms that could form part of the propofol infusion syndrome. The figures for failure on midazolam include a large group from one study (78/306 patients; Hayashi et al., 2007) in whom the reason for failure was not reported.

#### Breakthrough seizures

Once control was achieved, breakthrough seizures, defined here as seizures recurring after initial control and requiring switching of therapy, occurred at a rate of 3% on midazolam, 1.3% on propofol and 0% on barbiturate (in reports with sufficient detail). These figures do not include the greater number of patients who regained control after relapse by increasing the drug dosage and therefore not needing a switch of therapy: 7% on midazolam (21/281), 12% on propofol (6/50) and 6% on barbiturate (3/53). The data on breakthrough seizures are included in the Supplementary material. Not all reports provided the level of detail required and we recognize that some may not have been mentioned and that these figures may be artificially low.

### Table 2 Overall outcome of anaesthetic therapy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Thiopental/pentobarbital (n = 192)</th>
<th>Midazolam (n = 585)</th>
<th>Propofol (n = 143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>64% (123/192)</td>
<td>78% (458/585)</td>
<td>68% (97/143)</td>
</tr>
<tr>
<td>No control ever achieveda</td>
<td>5% (9/192)</td>
<td>16% (93/585)</td>
<td>11% (16/143)</td>
</tr>
<tr>
<td>Breakthrough seizures</td>
<td>0% (0/192)</td>
<td>3% (19/585)</td>
<td>1% (2/143)</td>
</tr>
<tr>
<td>Withdrawal seizures</td>
<td>9% (18/192)</td>
<td>&lt;1% (2/585)</td>
<td>6% (8/143)</td>
</tr>
<tr>
<td>Therapy failure because of side-effects</td>
<td>3% (5/192)</td>
<td>&lt;1% (1/585)</td>
<td>6% (8/143)</td>
</tr>
<tr>
<td>Death during therapy</td>
<td>19% (37/192)</td>
<td>2% (12/585)</td>
<td>8% (12/143)</td>
</tr>
</tbody>
</table>

*aExcluding 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.
Withdrawal seizures

Withdrawal seizures were reported less often on midazolam (0.3%) compared with 6% on propofol and 9% on thiopental/pentobarbital therapy (in reports with sufficient detail). In addition, when seizures did occur on tapering or withdrawal, a higher rate of regained control was reported in those patients in whom the drug was reintroduced on midazolam (93%) compared with the other two drugs (47% on propofol and 22% on barbiturate). The data on withdrawal seizures are included in the Supplementary material. As with breakthrough seizures, we have included only reports that provided sufficient level of detail and so these figures may be artificially low.

Death rates during infusion

The reported mortality rates were 19% on thiopental/pentobarbital infusions, 8% on propofol infusions and 2% on midazolam infusions. Comparison is complicated by the strong potential biases discussed above, which are likely to inflate the risk for barbiturate, and also because in some of the older reports on barbiturate therapy details were vague regarding the timing of death and some of these deaths may have occurred after the cessation of infusion. In relation to propofol, publication bias is also introduced by the inclusion of reports that focus on the ‘propofol infusion syndrome’.

Propofol infusion syndrome is a particular risk in prolonged infusion in children and in patients co-medicated with steroids or catecholamines. Iyer et al. (2009) found evidence of propofol infusion syndrome in 45% of 31 patients treated with prolonged infusions (mean 67 h) although a very broad definition of propofol infusion syndrome was used, which included patients with isolated symptoms such as unexplained hypotension and not necessarily the full blown syndrome. There is a high morbidity and mortality rate. Because of this risk, Iyer et al. (2009) recommend removal of propofol from their treatment protocol of status epilepticus. Other studies have found a lower risk and do not consider the use of propofol to be contraindicated provided there is careful monitoring, especially if the duration of infusion does not exceed 48 h (e.g. Power et al., 2011).

The studies included 920 patients, of all ages and a range of aetiologies. The median duration of therapy was 53 h (range 11–1200) on thiopental/pentobarbital, 32 h (range 0.5–432) on propofol and 16 h (range 10–240) on midazolam, perhaps reflecting the greater severity of the barbiturate cases. All drugs caused complications, most commonly hypotension and respiratory depression, which can be severe. Other life-threatening complications occurred with each of the drugs. The infusion doses varied considerably from report to report, ranging from 0.5 to 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 median duration (and range) of the status epilepticus before the onset of therapy was 16 h (1–720) for thiopental/pentobarbital, 18 h (10–600) for propofol and 4 h for midazolam (0.7–48).

There is one other published study of accumulated data from reports of anaesthesia in refractory status epilepticus (Claassen et al., 2002) in which 54 cases treated with midazolam, 106 with barbiturate and 33 with propofol therapy were reported. This study cites higher rates of withdrawal and breakthrough seizures. Methodology differed, however, and we were unable to determine how some figures had been calculated from our own scrutiny of the same publications.

Other anaesthetics

The published literature reporting outcome on ketamine infusion for super-refractory status epilepticus is very small—with only 17 reported cases, all of which were single case reports except one series of seven cases (Bleck et al., 2002). Control was achieved in 14 (82%) and it was postulated that the failure of control in the other three cases was due to insufficient dosage. The documentation of cases was slight and in only 10 were their sufficient details of type of status epilepticus or aetiology. Ketamine was used at a late stage in most cases (median duration of status prior to the use of ketamine was 672 h with a range 336–1680 h) and the median duration of therapy was 120 h (range 120–336). There was a loss of effect in one case and possible neurotoxicity in another. The long-term outcome was poor with death in seven and severe neurological deficit in three cases. The infusion dose range was 0.06–7.5 mg/kg/h.

The outcome of the use of the inhalational anaesthetics isoflurane and desflurane is reported in 27 episodes in seven publications. Initial control was reported in all cases. However, seizures recurred on withdrawal in 41% and two patients (7%) switched due to side-effects. As with ketamine, the inhalational anaesthetics were usually used late in the course of status epilepticus (a median duration of status prior to usage of 120 h and range 22–2472 h). The median duration of therapy was 45 h (range 1–2040). In the largest case series, isoflurane and desflurane were used in seven patients, and anaesthesia was maintained for a mean of 11 (range 2–26) days (Mirsattari et al., 2004). Four patients had good outcomes but three patients died subsequently. The therapy also had a high rate of complications including hypotension (7/7), atelectasis (7/7), infections (5/7), paralytic ileus (3/7) and deep venous thrombosis (2/7) (Mirsattari et al., 2004).

Antiepileptic drug therapy

It is universally recommended that antiepileptic drug therapy should be used concurrently with anaesthesia in refractory and super-refractory status epilepticus. However, the published outcome of the use of antiepileptics in this situation is restricted to 60 cases (in 10 reports) treated with topiramate, 10 (in two reports) with lamotrigine and 35 (in eight reports) with levetiracetam. There is no published outcome analysis of any other antiepileptic in refractory or super-refractory status epilepticus, despite very widespread usage of a large range of drugs. A range of modes of administration were used including instillation through a percutaneous endoscopic gastrostomy, nasogastric and rectal administration. In these small series, topiramate controlled the status in 62% (37/60), lamotrigine in 10% (1/10), pregabalin in 0% (0/2) and levetiracetam in 46% (17/39), although the definition of ‘control’ in lamotrigine cases [from the report of Goodwin et al. (2011)] was resolution of electrographic seizures within 4 h, which is a far stricter definition than used for other therapies. These figures,
coming as they do from small selected series, are not comparable. One patient died on topiramate and another on lacosamide therapy, and various complications occurred including metabolic acidosis on topiramate, angioedema on lacosamide, and rectal bleeding (during rectal administration) of levetiracetam. Where stated, the median duration of status before the drug was started was 144 h (range 0–720 h) for topiramate, 144 h (range 24–336 h) for lacosamide, 1632 h (range 744–2520 h) for pregabalin and 81 h (range 24–288) for levetiracetam. The dose of topiramate used was 2–25 mg/kg/day in children and up to 1600 mg/day in adults; of lacosamide was 100–400 mg/day in adults; of pregabalin was up to 600 mg/day in adults and of levetiracetam 13–70 mg/day in children and 250–6000 mg/day in adults.

Hypothermia

Hypothermia is now routinely used in several centres around the world for patients in super-refractory status epilepticus. The outcome of hypothermia in status epilepticus, however, is reported in only nine cases in four reports (one from 1984), all of whom obtained initial control and seven of the nine recovered. Endovascular cooling is the currently the preferred method in adults (but not necessarily children), and was used in four patients with external cooling used in the other five. The median duration of status prior to the initiation of hypothermia was 744 h (range 48–1440), and the median duration of therapy was 61 h (range 20–288). In the reported cases, there were significant complications including hypotension, electrolyte disturbance, acidosis, disseminated intravascular coagulation, thrombosis and thromboembolism, infection, bowel ischaemia, shivering and arrhythmias on rewarming. The core temperature in these reports was usually reduced to 32–35°C.

Magnesium infusion

Magnesium sulphate infusion is another widely used therapy in super-refractory status epilepticus although again the published evidence base-related outcome is remarkably small. The outcome of only three patients is reported, in one of whom the status epilepticus was controlled. All patients were young adults, two had mitochondrial disease. The time from the onset of status to the prescription of magnesium in these reports was between 144 and 1152 h and therapy was continued for between 48 and 168 h. The infusion rates varied between 2 and 6 g/h, with a target serum level in the report of Visser et al. (2011) of 3.5 mEq/l. However, in the case report by Fisher (1988), levels of magnesium were raised to extremely high levels (14.2 mEq/l) without control of seizures, and levels >8 mEq/l carry significant cardiovascular risks.

Pyridoxine infusion

Intravenous pyridoxine (as the hydrochloride) is an effective treatment in the rare patients with an inborn error of metabolism of pyridoxine. However, it has also been claimed that intravenous pyridoxine therapy may be effective in super-refractory status epilepticus when no clear deficit in pyridoxine metabolism is present, and pyridoxine is now routinely given in cases of super-refractory status epilepticus in young children. In fact, the outcome of therapy in non-pyridoxine-dependent patients is reported in only two cases, both of whom had low blood levels prior to therapy (one due to pregnancy and one to malnourishment), and although initial control was achieved in both cases, other therapies were given concurrently and attribution of success to pyridoxine is arguable. The infusion of pyridoxine alone carries no risk, although in some countries pyridoxine is only generally available as an infusion mixed with other vitamins (Pabrinex®) and this formulation carries a small risk of anaphylaxis. The doses used of pyridoxine were 180–600 mg/day.

Immunotherapy

Another treatment that is widely used in super-refractory status epilepticus is immunotherapy with steroids, intravenous immunoglobulins and plasma exchange. Outcome has been reported in only 21 cases in eight reports of patients without identified underlying immunological conditions. Of these, control of status was obtained in only 5%. In all cases, other therapies were also introduced concurrently and the effects on seizures may be delayed. It is thus difficult definitively to dissect the effects of immunotherapy from that of other treatment.

Resective neurosurgery

We have included resective neurosurgery in our analysis despite the fact that this is in many cases therapy directed at the cause per se, because the resection aimed to remove the epileptogenic zone not simply the lesion, and the extent of resection is often greater than the extent of the lesion. Thirty-six cases are reported, and in 33 the surgery resulted in control of the status epilepticus. In 21 cases, focal resection was carried out, in three focal resection and multiple subpial transection, in two focal resection and corpus callosectomy, in one multiple subpial transection corpus callosectomy and in eight some form of hemispherectomy. Pathology was identified in 25 cases and non-specific findings in 11.

Ketogenic diet

The use of the 4:1 ketogenic diet to control super-refractory status epilepticus has been reported in 14 cases of whom one later switched to the modified Atkins diet and one to a 3:1 diet, and a further two cases in whom the Atkins diet was used from the start. Initial control was observed in 12 of the 14 cases. In one case, the therapy was abruptly and inadvertently withdrawn and the epilepsy relapsed and the patient died. The age of the patients ranged between 4 and 49 years. The aetiology was established in three cases, and an additional nine (from a single report; Nabbout et al., 2010) were categorized as having FIRES (febrile infection-related epilepsy syndrome). The diet was used as a last resort in these cases, with the median duration of status epilepticus before the diet was started of 540 h (range 96–2424). The therapy was maintained in the long term in all patients (except the patient mentioned above) or changed to the modified Atkins diet.
**Other physical therapies**

A range of other physical therapies have been reported in recent case reports in the treatment of super-refractory status epilepticus. These include four case reports of patients treated with vagal nerve stimulation, with final control in all four, although in one patient pentobarbital was weaned 48 h before implantation and the status appeared to be resolving on the evening before the implantation (Patwardhan et al., 2005), and in the others the reported effect of vagal nerve stimulation was delayed with other therapies also given, rendering it impossible definitively to attribute improvement to the vagal nerve stimulation. One case of deep brain stimulation in the caudal zona incerta, in focal motor status epilepticus, is reported with resolution of the seizures. The outcome of eight patients (in six reports) treated with courses of ECT, with resolution of the status epilepticus in seven of the eight patients. Three to eight sessions of the ECT were given, with the treatment started at a median of 984 h (range 336–2472 h) after the onset of the status epilepticus, and with no complications except pneumonia in one case. There is a single convincing report of immediate control of super-refractory status by CSF drainage although with subsequent relapse (Korhmann et al., 2006). Repetitive transcranial magnetic stimulation has been used experimentally and outcome reported in cases of simple partial status epilepticus and epilepsia partialis continua. Classical music is another therapy that has been used in non-convulsive status epilepticus. Neither of the two latter therapies have been reported in convulsive status epilepticus and so are not considered further here.

**Long-term outcome**

In this article, we have focused our outcome assessment on the immediate control of seizures as the primary end-point of each therapy. In a total of 596 cases, the long-term outcome could also be ascertained, divided into five broad categories, and the results are shown in Table 3. Overall, 35% of the patients died. The death rate was higher in patients who had been treated with thiopental/pentobarbital (46%) compared with propofol (36%), midazolam (34%) and ketamine (44%) but this likely reflects the potentially severe biases discussed above. The death rate in treatment of those that had been treated with all other therapies ranged from 0 to 36%, except a rate of 67% in those treated with magnesium and a rate of 50% in those treated with levetiracetam.

In our view, it is not possible from these figures to draw any conclusions about whether any specific therapy is responsible for a particularly high or low rate. Furthermore, long-term mortality is known to be related not so much to the treatment used as to the underlying aetiology (probably the main determinant) and also the duration of status epilepticus.

**Discussion**

The most striking conclusion from this exploration of the literature is the poor quality of the outcome data, which indeed is so inadequate that only broad conclusions can be drawn from this analysis. The assessment of each therapy is severely compromised by a number of points.

(i) The lack of randomized or controlled studies: in this review we found only a single randomized study, and this failed to recruit (see above). Almost all the other studies were either case reports or retrospective series.

(ii) The small number of individuals treated: many treatments discussed, even if very widely used in routine practice, are based on a very small number of published cases. Indeed, apart from the three commonly used anaesthetics (propofol, midazolam or pentobarbital/thiopental), none of the treatments reviewed here have a total published outcome data in more than 40 patients, and most in less than 10 patients. This is an extraordinary state of affairs.

(iii) Co-medication and changing doses of co-medication. Therapies in the super-refractory period of status are almost always given in parallel, and assessment of a therapy is often complicated by concurrent changes in dosages, or physical parameters, of another.

(iv) Delay in responses. Reports of responsiveness for some therapies include patients who responded days or weeks after the application of treatment. This applies to the studies of vagal nerve stimulation, ECT, antiepileptic drugs, ketogenic diet neurosurgery and immunotherapy. Furthermore, concomitant therapy is also often changed. This makes causal attribution very difficult to make.

(v) 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.

(vi) Finally, refractory status epilepticus is heterogeneous and its ultimate prognosis depends on factors other than treatment such as age and aetiology (Neligan and Shorvon, 2010, 2011). These further complicate any assessment of individual therapies.

This is all the more regrettable given the severe nature of refractory status epilepticus, with its mortality rate of 35% and its high morbidity. It is an inescapable conclusion that our current approaches to therapy are based on an inadequate literature with large potential biases.

<table>
<thead>
<tr>
<th>Table 3 Long-term outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>Deaths</td>
</tr>
<tr>
<td>Severe neurological deficit</td>
</tr>
<tr>
<td>Mild neurological deficit</td>
</tr>
<tr>
<td>Undefined neurological deficit</td>
</tr>
<tr>
<td>Recovery to baseline</td>
</tr>
</tbody>
</table>

*In the reports of 596 cases (51% of the total of 1168), the long-term outcome was recorded. In the other 575 cases, no long-term outcome data were provided.*
Recommendations for treatment approach and protocol

These drawbacks hinder the making of any definitive recommendations about therapy. A treatment protocol has been suggested elsewhere (Shorvon and Ferlisi, 2011). Our analysis of outcome does not provide definitive guidance on how appropriate this approach is. However, a number of broad conclusions can be drawn.

First-line therapy

This is a therapy that should be applied to every case, in conjunction with the full panoply of ITU care and support and with treatment of the underlying cause (Shorvon and Ferlisi, 2011).

Anaesthetics

General anaesthesia remains the backbone of therapy in refractory and super-refractory status epilepticus. Our analysis confirms that this is an effective therapy in the majority of cases. Immediate control of refractory status epilepticus is achieved in two-thirds of cases, and the rate of breakthrough and withdrawal seizures is lower than often quoted. Although the raw data show a higher mortality rate on barbiturate therapy, we consider this difference to be due to selection bias and that there is no reliable support for marked differences in mortality between treatments. Moreover, mortality in status epilepticus is largely determined by the underlying aetiology (Neligan and Shorvon, 2010) and with modern ITU practice, iatrogenic mortality rates should be low. The three anaesthetic drugs conventionally used have a number of important differences. Their advantages and disadvantages have been reviewed elsewhere (Shorvon and Ferlisi, 2011), and these findings are summarized in Table 4. Due to the inherent biases in outcome data, comparison of the three drugs can be made only cautiously, but a number of recommendations can be securely made. These are summarized in Table 5.

Ketamine is reserved as a second-line drug because of the very limited clinical evidence base and the potential neurotoxic effects. There is also one case report where the development of cerebral atrophy, after status epilepticus, is postulated to have been due to ketamine therapy (Ubogu et al., 2003), although status epilepticus itself can cause cerebral atrophy and this could be an alternative explanation in this case.

Table 4 Advantages and disadvantages of anaesthetics used in status epilepticus

<table>
<thead>
<tr>
<th>Anaesthetic</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopental/pentobarbital</td>
<td>- strong antiepileptic action;</td>
<td>- problematic pharmacokinetics—zero-order kinetics, profound tendency to accumulation, long recovery time, hepatic metabolism, autoinduction, drug-drug interactions; hypotension, cardio-respiratory depression; and pancreatic and hepatic toxicity.</td>
</tr>
<tr>
<td>Midazolam</td>
<td>- antiepileptic action; and</td>
<td>- may be less effective than other anaesthetics; hypotension, cardio-respiratory depression; risk of hepatic and renal impairment; and risk of tolerance and breakthrough seizures (probably overestimated).</td>
</tr>
<tr>
<td></td>
<td>- only benzodiazepine with pharmacokinetic properties suitable for prolonged infusion without accumulation.</td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>- excellent pharmacokinetic properties including very rapid onset and recovery even after prolonged infusion allowing ease of control of anaesthesia;</td>
<td>- propofol infusion syndrome, especially in children; pain at the injection site; and difficulty in differentiating drug-induced involuntary movements and seizures.</td>
</tr>
<tr>
<td></td>
<td>- no drug interactions; and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- less hypotension and cardio-respiratory depression than barbiturate or midazolam anaesthesia.</td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>- no cardiodepressant or hypotensive action; and</td>
<td>- very limited published experience; and possible neurotoxicity.</td>
</tr>
<tr>
<td></td>
<td>- anti-glutaminergic action.</td>
<td></td>
</tr>
</tbody>
</table>
In situations where anaesthetics are being continued, the need for anaesthesia exceed the risks of seizures and in this situation, anaesthesia should be weaned slowly on reversal. This decision needs to be tailored to individual circumstances. Prolonged anaesthesia carries increasing iatrogenic risks, and skilled ICU care and monitoring for complications is mandatory. It is possible that in very prolonged status epilepticus (weeks or months) that the risks of anaesthesia exceed the risks of seizures and in this situation, consideration could be given to reversing the anaesthesia altogether. We know of no data on this point, which deserves further study.

### Therapies in convulsive status epilepticus

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#### Table 5 Recommendation for anaesthetic use in refractory and super-refractory status epilepticus (adults)

<table>
<thead>
<tr>
<th>Anaesthetic</th>
<th>Dose</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopental/ pentobarbital</td>
<td>Thioental: 2–3 mg/kg</td>
<td>First-line therapy in severe cases.</td>
</tr>
<tr>
<td></td>
<td>Maintenance dose: 3–5 mg/kg/h</td>
<td>Avoid in situations where pharmacokinetic interactions would be detrimental.</td>
</tr>
<tr>
<td></td>
<td>Pentobarbital:</td>
<td>Avoid in hepatic disease, myasthenia gravis, porphyria, severe haemorrhage or burns, cardiovascular disease, adrenocortical insufficiency.</td>
</tr>
<tr>
<td></td>
<td>Loading dose: 5–15 mg/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maintenance dose: 0.5–3 mg/kg/h</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>Loading dose: 0.1–0.2 mg/kg</td>
<td>First-line therapy in most cases.</td>
</tr>
<tr>
<td></td>
<td>Maintenance dose: 0.1–0.4 mg/kg/h</td>
<td>Avoid in hepatic or renal disease, myasthenia gravis, porphyria.</td>
</tr>
<tr>
<td>Propofol</td>
<td>Loading dose: 3–5 mg/kg</td>
<td>First-line therapy in complex cases where ease of use and pharmacokinetic properties are important.</td>
</tr>
<tr>
<td></td>
<td>Maintenance dose: 5–10 mg/kg/h</td>
<td>Use where other drugs cause problematic hypotension.</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Loading dose: 1–3 mg/kg</td>
<td>Second-line therapy especially where hypotension or cardiorespiratory depression is problematic.</td>
</tr>
<tr>
<td></td>
<td>Maintenance dose: up to 5 mg/kg/h</td>
<td></td>
</tr>
</tbody>
</table>

The doses reflect our clinical practice, but higher doses are sometimes quoted in the literature, for instance midazolam 0.2–0.6 mg/kg/h and ketamine up to 7.5 mg/kg/h (Rossetti and Lowenstein, 2011).

There are formidable technical and logistical difficulties in maintaining prolonged inhalational anaesthesia in a neurological ICU setting and in our opinion, these and the high rate of complications preclude the use of these drugs in most clinical situations.

It would be usual initially to reverse anaesthesia every 24–48 h and if seizures continue, then to re-establish anaesthesia (cycling). Such cycles should be repeated several times. If the status continues to recur, the duration of individual cycles can be increased, and anaesthesia continued for up to 5 days at a time. The anaesthesia should be weaned slowly on reversal. This decision needs to be tailored to individual circumstances. Prolonged anaesthesia carries increasing iatrogenic risks, and skilled ICU care and monitoring for complications is mandatory. It is possible that in very prolonged status epilepticus (weeks or months) that the risks of anaesthesia exceed the risks of seizures and in this situation, consideration could be given to reversing the anaesthesia altogether. We know of no data on this point, which deserves further study.

### Antiepileptic therapy

Antiepileptic drugs should always be given, so that when the anaesthetic agent is withdrawn there is adequate antiepileptic cover (in situations where anaesthetics are being continued, the need for antiepileptics is less). There are unfortunately no reliable data suggesting that any particular antiepileptic drug is better than another, nor any evidence concerning regimes or therapeutic approaches. Although many of the antiepileptics are widely used, the only published literature in super-refractory status epilepticus refers to topiramate (60 cases), levetiracetam (35 cases), pregabalin (2 cases) and lacosamide (10 cases).

No conclusions regarding choice of drug can be made on this basis. However, by analogy with antiepileptic drug therapy in other situations, the following recommendations can be made

<table>
<thead>
<tr>
<th>Choice of drug regimen depends on clinical context</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polytherapy with two antiepileptic drugs</td>
</tr>
<tr>
<td>High-dose regimens</td>
</tr>
<tr>
<td>Avoid frequent switching</td>
</tr>
<tr>
<td>Favour antiepileptic drugs with low interaction potential</td>
</tr>
<tr>
<td>Favour antiepileptic drugs with predictable kinetic properties</td>
</tr>
<tr>
<td>Favour antiepileptic drugs without renal or hepatic toxicity</td>
</tr>
<tr>
<td>Avoid GABAergic antiepileptic drugs</td>
</tr>
</tbody>
</table>

(Table 6): (i) polytherapy with no more than two drugs, used at high doses. Morbidity will rise with more extensive drug regimes; (ii) frequent switches should not be made, as rapid withdrawal can exacerbate the tendency for seizures to occur (rebound seizures), increase side-effects, risk allergic reactions and also cause pharmacokinetic changes; and (iii) the choice of drug will depend on the clinical context. However, it seems sensible to use powerful antiepileptics; to avoid those with a primarily GABAergic mechanism of action (e.g. benzodiazepines, barbiturates) as there is evidence of loss of efficacy as status epilepticus becomes more prolonged and because the anaesthetic drugs themselves have much more powerful GABAergic effects. Where possible, drugs with low interaction potential and predictable kinetics should be used, and antiepileptics with strong allergenic potential and potential renal or hepatic toxicity should be avoided. Levetiracetam, topiramate, pregabalin and lacosamide are possible options, given through the nasogastric tube or percutaneous endoscopic gastrostomy. The target dose should be the high maintenance dose used in routine oral antiepileptic drug therapy.
Second-line therapy

This is a therapy that can be applied in those cases in which first-line therapy is not controlling the status epilepticus and should be considered at some point after the initiation of anaesthesia and antiepileptic drug therapy. How long after will depend on individual circumstances, but the longer the seizures persist the worse the functional outcome. There are a number of choices and approaches, and there is no clear guidance about which to choose or in what order. Based on this review, therapy should be selected from the following.

Hypothermia

As mentioned above, hypothermia is routinely used in some centres for the treatment of status epilepticus, despite an extremely small evidence base. It is a therapy that deserves further study, not least because of the solid experimental evidence of neuroprotective as well as seizure-terminating properties. However, there are significant complications and serious side-effects, and it is a therapy that should be embarked upon only in experienced centres. The level of hypothermia is also uncertain, and it has been suggested that only mild hypothermia is effective (Rossetti, 2011). In which cases it should be employed, or at what stage, unfortunately is unclear, but it does seem reasonable to consider this as a second-line therapy, in resistant cases, with target temperatures between 32 and 35°C and the hypothermia continued in the first instance for 24–48 h.

Magnesium infusion and pyridoxine infusions

The widespread use of magnesium infusion is based on the proven efficacy of magnesium in eclamptic seizures, and also supported by a small body of experimental work. Indeed, there have been sporadic case reports of its clinical use since 1901. The administration of magnesium in patients with super-refractory status epilepticus that are not responding to therapy carries no major risk, although hypotension and PR interval prolongation are reported and caution is advised when co-administered with barbiturates or benzodiazepines due to a risk of enhanced respiratory depression, and when co-administered with digoxin or calcium channel blockers. Also, at high doses the neuromuscular blocking effects may mask convulsive movements, which can be clinically misleading. It seems reasonable to infuse magnesium at a dose 2–6 g/h to obtain a serum level of 3.5 mmol/l. If this is effective, the infusion should be continued, and ceased if ineffective.

In young children, pyridoxine is also widely administered on the basis that deficiency may be difficult to detect and can be disastrous if overlooked. Furthermore, it is possible that there is effectiveness in the absence of deficiency, although there is little evidence that this is the case. The infusion of pyridoxine alone is entirely safe, although the infusion of the combined vitamin preparations (Pabrinex®) carry a small risk of anaphylaxis. A reasonable dose would be 180–300 mg.

We consider that these therapies should have marginal evidence of efficacy but as they carry little risk and are relatively easy to administer, they should be used as second-line therapies in super-refractory status epilepticus.

Immunological therapy

The outcome of therapy with steroids, intravenous immunoglobulin and plasma exchange, based on this literature review, is poor, with only 5% of patients gaining control. However, this approach is widely used despite the very limited evidence base, and anecdotal clinical experience is much more promising. This use is based on two theoretical propositions. First, it is possible that some cases of cryptogenic refractory status epilepticus are caused by underlying occult auto-immune or immunological conditions. This proposition is encouraged by the finding of cases due to newly discovered antibodies including the anti-NMDA receptor antibodies and the voltage-gated potassium antibodies. Second, is the possibility that inflammatory mechanisms occur at the epilepsy focus, resulting in epileptogenesis, and there is growing experimental evidence of the importance of such inflammation (Vezzani and Ruegg, 2011). Thus, in our opinion, a trial of immunological therapy is worthwhile as a second-line therapy in patients with super-refractory status epilepticus, without a history of previous epilepsy and in whom no aetiology has been found. However, there is an urgent need for more systematic study of this line of therapy.

A typical regimen would be to start therapy with high-dose steroids and a course of intravenous immunoglobulin or plasma exchange. The steroids should be given for 3 days at a high dose (1 g/day in adults) and continued at lower doses (1 mg/kg/day) for a period of ~1 week, and continued if there is a response. In addition, a course of intravenous immunoglobulin over 5 days, at a dose of 0.4 g/kg/day, or plasma exchange, can be tried. If there is a response, long-term steroids and repeated courses of intravenous immunoglobulin can be used.

Ketogenic diet

The ketogenic diet is easy to administer in super-refractory status epilepticus, either through the nasogastric tube or percutaneous endoscopic gastrostomy. Ready-made solutions with 4:1 commercial preparation (KetoCal) are most commonly used. The evidence base, however, is very small (12 cases of 4:1 ketogenic diet and two cases of the modified Atkins diet) although the recorded response of the cases was convincing. It carries certain risks and is contraindicated in cases of pyruvate carboxylase and β-oxidation deficiencies. It should, furthermore, probably not be used with propofol anaesthesia or with steroid co-administration. A 4:1 diet with the initial complete avoidance of glucose is recommended. Details of the administration of the diet can be found in Nabbout et al. (2010).

Emergency neurosurgery

In the published cases (36 in total), a good long-term outcome was reported in 27 (75%). The type of surgery included focal resection, multiple subpial transection, corpus callosectomy and hemispherectomy (sometimes in combination). Thus, emergency neurosurgery has, in our opinion, a small place as a second-line therapy in super-refractory status epilepticus, where there is a clear-cut electrographic focus and a lesion causing the epilepsy, but in no other situation.
Third line—last resort therapies

The data on these are so deficient that assessing their place is not possible. At present, they should be reserved for consideration in those very resistant cases where first and second-line therapies have proved ineffective. With more experience, it is possible that some will become second-line therapies.

Electroconvulsive therapy

There are a few reports of effectiveness of ECT, although all patients had withdrawal or reduction of anaesthesia to allow ECT to be given and it is possible that this in itself resulted in the resolution of the status epilepticus, not least as between—three and eight sessions were required to control the seizures and the response was therefore observed after days of therapy. Nevertheless, this is a therapy used in several centres worldwide and should be considered as a third-line treatment, and where used, daily sessions should be given for between 3 and 8 days.

Cerebrospinal fluid drainage and other therapies

There is one modern report of two episodes of CSF drainage in the same patient. The first procedure was highly effective (Korhmann et al., 2006). Exactly how such a therapy would result in control of status epilepticus is unclear, but it is possible it removes inflammatory or other compounds from the CSF or, less likely, acts via changes of intracranial pressure dynamics. It is a therapy that was widely used up until the 1940s at least, and was reported to be ‘serviceable’ by S.A. Kinnier Wilson in his textbook (1940). It would be worth considering at least, as a last resort therapy, in severe super-refractory status epilepticus.

In relation to vagal nerve stimulation, deep brain stimulation and repetitive transcranial magnetic stimulation, there is, in our opinion, no clear evidence of any efficacy from these therapies, each of which has drawbacks and hazards and so cannot be recommended at present.

Treatment directed at the cause of the status epilepticus, and ITU therapy

In all patients, treatment directed at the cause of the status is vital and the long-term outcome is to a large extent dependent on this. Skilled ITU care is also vital, with EEG monitoring and in some cases intracranial pressure monitoring (Schmutzhardt and Pfaußer, 2011; Smith, 2011). There are no studies of the value of neuroprotectants and these would be worth pursuing in the future.

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Supplementary material

Supplementary material is available at Brain online.

References


Appendix 1

Details of the literature used as the basis of this review are published elsewhere (Shorvon and Ferlisi, 2011). Of these 159 papers, 121 published since 1981 reported outcome data in 1061 patients in sufficient detail. These papers form the evidence base of this review and are listed below:


