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# Status epilepticus - update on diagnosis and treatment

# Stan padaczkowy - rozpoznanie i leczenie

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**Abstract**

*Epilepsy is the most common serious neurological disorder, affecting approximately 1 in 150 people, and status epilepticus (SE) is sometimes described as the maximal expression of epilepsy, being associated with both short- and long-term significant mortality and morbidity. There are almost as many types of status as there are of the seizures. SE describes a unique pathological state, during which seizures tend to become self-perpetuating. The definition of SE shortened in the last years from 30 min in the guidelines of the Epilepsy Foundation of America's Working Group on Status Epilepticus to 10 min in the VA Cooperative Trial, and recently in the operational definition of SE was shortened to 5 min, which reflects the need to find a definition of SE which will not delay therapeutic intervention. In this article we present current knowledge on diagnostics and treatment of SE and discuss possible therapeutic options, with emphasis on the role of new antiepileptic drugs.*

**Streszczenie**

*Padaczka jest najczęstszym schorzeniem neurologicznym, występującym u 1 na 150 osób, a stan padaczkowy (SP) jest czasem opisywany jako maksymalna ekspresja padaczki i jest związany ze znaczną krótko- i długoterminową śmiertelnością. Istnieje prawie tak dużo typów stanu padaczkowego jak rodzaju napadów padaczkowych. Stan padaczkowy jest unikalnym stanem patologicznym, w którym napady mają tendencję do ciągłego utrzymywania się. Definicja stanu padaczkowego uległa skróceniu z 30 minut w zaleceniach Epilepsy Foundation of America's Working Group on Status Epilepticus, do 10 minut w VA Cooperative Trial, a ostatnio stosowana jest operacyjna definicja stanu padaczkowego, który można rozpoznać jeśli drgawki trwają powyżej 5 minut. Odzwierciedla to jednocześnie potrzebę znalezienia definicji stanu padaczkowego, która nie spowoduje opóźnienia interwencji terapeutycznej. Powszechnie znane są robocze definicje stanu padaczkowego wczesnego (do 30 minut), utrwalonego (30-60 minut) oraz opornego na leczenie, a podział ten jest wynikiem ewolucji zmian patolofizjologicznych w przebiegu SP. W poniższym artykule przedstawiamy aktualne postępowanie diagnostyczno-terapeutyczne w SP z uwzględnieniem roli nowszych leków przeciwdrgawkowych takich jak lewetiracetam.*

*Key words:* epilepsy, status epilepticus
*Słowa kluczowe:* padaczka, stan padaczkowy

## Introduction

Epilepsy is the most common serious neurological disorder, affecting approximately 1 in 150 people [1], and status epilepticus (SE) is sometimes described as the maximal expression of epilepsy, being associated with both short- and long-term significant mortality and morbidity. There are almost as many types of status epilepticus as there are of seizures. SE describes a unique pathological state, during which seizures tend to become self-perpetuating. The definition of SE shortened from 30 min in the guidelines of the Epilepsy Foundation of America's Working Group on Status Epilepticus to 20 min [2], to 10 min in the VA Cooperative Trial [3], and recently in the operational definition of SE to 5 min [4]. This reflects the need to find such a definition of SE which will not delay therapeutic intervention. Early therapeutic intervention diminishes the risk of SE-induced neuronal injury [5,6] and of the time-dependent development of pharmacoresistance [7,8]. Once established, status epilepticus is a condition that continues to evolve and change over time.

## History

Descriptions of status epilepticus appear throughout the historical medical literature [9]. The advanced research on status epilepticus began in the 19th century, in London (at the National Hospital for the Paralysed and the Epileptic) and in Paris (at the Salpêtrière and Bicêtre Hospitals). The classical descriptions of untreated status come from such neurologists as Charcot, Bourneville, Hughlings Jackson and Gowers, who not only identified the natural course of untreated status, but also described the subtypes of status, and recognized

that they may represent different diseases. With the invention of the electroencephalogram (EEG), in the 1920s, that the electrographic manifestations of status epilepticus were described, and this 'dominated research for the next 50 years' [9].

## Definitions

Working definitions of early (up to 30 min), established (30–60 min) and refractory (longer than 60 min) status are commonly applied, and derive from the known pathophysiological evolution of status epilepticus. Early status epilepticus is defined as continuous seizures or intermittent seizures without full recovery of consciousness between seizures, lasting more than 5 minutes. Cerebral metabolic demand is generally sustained during phase 1 in tonic-clonic status, but not during phase 2, which is accompanied by profound metabolic complications. Established status epilepticus is defined as clinical or electrographic seizures lasting more than 30 min without full recovery of consciousness between seizures. The term subtle status epilepticus was coined by Treiman [10] to describe the late, burned-out stage of SE during which both the motor and electroencephalographic (EEG) expression of seizures becomes less evident. Cerebral metabolic demand is generally sustained during phase 1 tonic-clonic status, but not during phase 2, which is accompanied by profound metabolic complications [11]. The combination of metabolic decompensation and the direct neurotoxic effects of ongoing seizure activity contribute to an association between long duration of status and poor outcome, hence the slogan 'time is brain'.

## Diagnosis

A confident diagnosis is not always possible on clinical symptoms alone, and the biggest problem may be functional non-epileptic seizures that may closely resemble epileptic seizures, even to the most experienced observer. The diagnosis and management of functional non-epileptic seizures are not a subject of this article, but it is worth noticing that some patients with tonic-clonic status have only minor motor features. Fever, tachycardia, leucocytosis and acidosis are often present, but are nonspecific, and usually tend to occur late. In an ideal situation, EEG would be available at this early point in making the diagnosis, but is not often achievable. The inappropriate treatment of non-epileptic seizures carries a significant risk of avoidable iatrogenic complications, including respiratory arrest and admission to ITU (with attendant consequences of invasive treatment there). However, delayed treatment of tonic-clonic status can be equally dangerous. On balance, where there is doubt, so long as the possibility of functional attacks has been considered but seems less possible than the risks of inappropriate treatment, rapid and adequate treatment as for tonic-clonic status is probably the best option. Identification of normal EEG alpha rhythm in the unconscious patient between convulsive movements effectively excludes tonic-clonic status, and the distinction between this and postictal slowing is recognizable with limited training.

## Time-dependent pharmacoresistance

A unique feature of self-sustaining SE (SSSE) is the progressive, time-dependent development of pharmacoresistance: the potency of benzodiazepines may decrease 20-fold in 30 min of SSSE; phenytoin also loses potency, but more slowly [12]. By contrast, even late in its course, NMDA blockers continue to be effective in stopping SSSE [12]. The same dose of benzodiazepine which easily blocks SE when given early is far less effective when given late. However, ketamine easily terminates established SE.

## Management of tonic-clonic status epilepticus

Nursing care is important at preventing injury and monitoring and maintenance of basic physiological parameters such as heart rate and rhythm, respiratory rate, blood pressure and testing for blood sugar. High-flow oxygen should be provided, the airway secured (trismus of the masseter muscles may make this difficult, in which case a nasopharyngeal airway is a reasonable alternative), a wide-bore cannula inserted, and fluid resuscitation started. Initial investigations should include full blood count, urea and electrolytes, calcium, magnesium, liver enzymes, blood sugar, and blood cultures if infection is suspected. Serum for drug levels should always be taken at the outset, even if at that stage there is no detailed history. Specific AED levels can be measured later from stored serum, and this might provided essential information about the cause of the status.

The inappropriate treatment of non-epileptic seizures carries a significant risk of iatrogenic complications, including respiratory failure or arrest and admission to ITU. In an audit of treatment of status epilepticus, 44% of patients presenting to ITU had received inadequate prior doses of AEDs [13], mainly due to underestimating the amount of phenytoin necessary as a loading dose. However, delayed treatment of tonic-clonic status can be equally dangerous. When to initiate treatment will vary for individuals, but might include preventative treatment (e.g. clobazam 10–20 mg/day orally, not available in Poland) during known high-risk periods (e.g. menstruation or

infection), or parenteral treatment if a prolonged (> 5 minute) convulsion occurs (rectal diazepam 10-20 mg in adults). If there is any suspicion of hypoglycemia, then 50 ml of 50% iv dextrose or glucose should be given. Similarly, if alcohol dependence is suspected, then thiamine replacement should be given iv, particularly if iv glucose has also been prescribed (sudden glucose loads can precipitously lower circulating thiamine levels). Lorazepam is the drug of choice, once intravenous access is available, in all current guidelines. Intravenous diazepam has been used traditionally, and although it has a rapid onset of action, it is quickly redistributed into fatty tissue often leading to rebound seizures. If benzodiazepines fail, currently approved treatment for established status include phenytoin, phenobarbitone and fosphenytoin [14].

*Phenytoin* has a very high pH (~12), so can cause significant cellulitis if extravasation occurs, and it must be diluted in 0.9% saline (rather than dextrose) to avoid crystallization. Also it must be administered through a side-arm (or a separate iv line) to avoid reaction with other iv drugs and fluids, usually over 20 min. All these factors can mean several minutes between the decision to give phenytoin, and the patient receiving it. There is also a risk of cardiac arrhythmias and hypotension with parenteral phenytoin, particularly if given quickly, and patients require cardiac monitoring. Purple hand syndrome, a rare skin reaction to parenteral phenytoin (consisting of swelling, pain and discolouration of the skin) is a potential problem, but this can be avoided by the use of proximal, large-calibre veins for the iv infusion, and in any event it is probably much less common than previously thought [15].

Phosphenytoin has a lower pH (and thus causes fewer problems in solution), it does not cause purple hand syndrome, and there is less risk of cardiac and hypotensive complications (although cardiac monitoring is recommended during its administration). It can be given much more quickly than phenytoin, and even intramuscularly if iv access is not available [16]. However, the dosage nomenclature (1.5g fosphenytoin= 1g phenytoin = 1 PE, or phenytoin equivalent), designed to facilitate its use as a phenytoin replacement, has sometimes led to confusion and administration errors. Taking this into consideration, together with cost (it is at least 10 times more expensive than phenytoin) [17], it has never become popular, although there is substantial clinical experience with it elsewhere [18].

*Phenobarbitone*, one of the oldest AEDs, has a number of practical advantages: it requires less dilution and can be injected more quickly (iv push directly over 10 min) – an important consideration when time matters; and although it also has the potential for hypotension, there are fewer local adverse effects, and it may have faster brain penetration and onset of action than phenytoin. To support this, an open study of 36 patients comparing diazepam plus phenytoin, and phenobarbitone plus optional phenytoin [19] found a significantly shorter response time in controlling seizures (up to 14 min faster) with phenobarbitone, without more complications.

Intravenous levetiracetam and valproate are sometimes used in neurological centres, and have shown to be safe and effective in status epilepticus [19,20]. Since its introduction in 2006, levetiracetam has been tested not only in the treatment of refractory epilepsy but also in the treatment of status epilepticus, this usually after ineffective treatment with beznodiazepines given intravenously. Levetiracetam has mostly been tested in SE at a dose of 1000 to 2000 mg. Additionally, the drug is well tolerated when injected in fractionated form, thus in moderate doses may be an efficacious alternative for the treatment of focal and myoclonic SE, especially in elderly persons with concomitant medical disorders. Data from single centers reveal that the drug has rather been effective in simple focal SE, complex focal SE and myoclonic SE than in nonconvulsive and subtle SE [20]. However data from some centers show also effectiveness of the drug in secondary generalized clonic status epilepticus [21]. The drug has rapid onset of action, the absence of hepatic cytochrome P 450-dependent metabolism and drug interactions, the relative lack of sedation and contraindications. These features are main advantages of the intravenous drug over phenytoin or sodium valproate, thus indicating levetiracetam to be used in elderly patients who usually take several medications or have hepatic or renal failure. Factors indicating poor prognosis when using levetiracetem in SE are: cryptogenic SE, primarily generalized status epilepticus, previous politherapy with i.v. phenytoin or sodium valproate and SE due to brain anoxia [22].

There is also accumulating evidence on the effects of sodium valproate in the treatment of the partial SE [23,23,25,26,29]. However further controlled studies are needed to assess the efficacy of intravenous VPA in the treatment of this rare condition.

When it comes to refractory status, there is even less evidence on which to base treatment decisions. Expert consensus and all current guidelines advise that if treatment is still not controlling seizures at this stage (between 30 and 60 min), the patient should be transferred to ITU for general anesthesia, both to suppress seizures and for the

management of the systemic adverse effects of the epilepsy and the drugs being used to suppress it. Three agents are in common use at present: thiopenthal, propofol and midazolam. If seizures recur, the diagnosis should be revisited, both in terms of whether this is truly epilepsy (necessitating EEG in the unconscious patient), and with respect to etiology. Even in patients with known epilepsy, magnetic resonance imaging, and cerebrospinal fluid (CSF) examination, should be undertaken or repeated to exclude new pathology.

### Maintenance anti-epileptic drugs

Together with emergency management, attention must be given to maintenance anti-epileptic therapy. In patients known to have epilepsy, their usual AED regime should be maintained throughout, using iv or nasogastric tube administration in those who are unconscious for any prolonged period. Sometimes modification of dosage may be required, depending perhaps on AED levels, and, unless there is an obvious remedial precipitant, most patients should have an urgent review of their treatment by a neurologist. In patients presenting status epilepticus *de novo*, because the underlying cause may not be completely reversible, and because of the high risk of developing epilepsy following an episode of status, most experts recommend AEDs for at least 3-6 months, often longer and even in the absence of recurrent seizures depending on the cause. Present recommendation is to initiate oral maintenance therapy, preferably either valproate or carbamazepine [14] in line with current guidelines within the first few hours after presentation, in anticipation that by the time the acute situation has resolved and phenytoin or phenobarbitone levels have dropped, there will be sufficient level of the maintenance AEDs to 'take over' control.

### SE-induced epileptogenesis

It is also likely that status in itself plays a role in epileptogenesis: many of the animal models of chronic epilepsy use chemically or electrically induced status to trigger the later development of spontaneous recurrent seizures, without necessarily any additional structural insult [27]. In man, around 12% of patients with epilepsy have status at presentation, and episodes of status can change seizure type in established epilepsy [28]. Probably, it is one of the most important problems associated with SE.

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