Standards of care for non-convulsive status epilepticus : belgian consensus recommendations

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Abstract

Non-convulsive status epilepticus (NCSE) makes up around one-third of all cases of SE, affecting approximately 1,000 to 4,000 individuals per year in Belgium. Compared with convulsive SE, NCSE has received considerably less attention, is underdiagnosed and undertreated. However, if recognised, NCSE can however be treated successfully. A workshop was convened by neurologists from major Belgian centres to review the latest information on NCSE and to make recommendations on diagnosis and treatment. These recommendations are not only intended for neurologists, but also for primary care physicians and physicians in intensive care units. NCSE should be suspected whenever cases of fluctuating consciousness or abrupt cognitive or behavioural changes are noted. Confirmation of diagnosis by EEG should be obtained wherever possible. In view of the often subtle clinical signs, EEG is also vital for monitoring treatment outcome. Non-comatose patients should generally be treated in a neurology ward since referral to an ICU is unnecessary. First-line treatment should be an intravenous benzodiazepine. For many patients who fail to respond to benzodiazepines, intravenous valproate will successfully abrogate seizure activity. Intravenous phenytoin can be used in patients with focal NCSE in whom valproate is contraindicated or ineffective. Time and care should be spent in identifying an appropriate and effective antiepileptic drug regimen without recourse to anaesthesia. For comatose patients, treatment intensity should be graded according to epilepsy history, general medical state and prognosis. In some patients, intensive remedial measures may allow rapid resolution of NSCE, whereas in more vulnerable patients, such treatment may be counterproductive.

Key words : Epilepsy ; status epilepticus ; diagnosis ; treatment ; consensus ; non convulsive.

Introduction

This article reflects the discussions and recommendations of a two-part consensus meeting which brought together eight experts to assess the management of non-convulsive status epilepticus (NCSE). The aim of the consensus meeting was to review recent literature data in the field, as well as current clinical practice in Belgium and, on the basis of this information, to draft pragmatic guidelines for the treatment of this condition. The care of babies and small children with non-convulsive status epilepticus, which requires special considerations, is excluded as being outside the scope of these guidelines, as well as continuous spike-and-wave during slow sleep (CSWS), sometimes considered as electrical status epilepticus during sleep (ESES). The meeting follows a previous one in which consensus treatment guidelines for convulsive status epilepticus were put forward (1).

Background

Non-convulsive status epilepticus (NCSE) has been defined in a recent consensus workshop organised by the Epilepsy Research Foundation (ERF) as "*a term used to denote a range of conditions in which electrographic seizure activity is prolonged and results in non-convulsive clinical symptoms*" (2). This is clearly an operational definition and highlights our lack of knowledge of the aetiology of NCSE. The term relates to a common schematic electro-clinical presentation of a variety of underlying epilepsy syndromes. NCSE has traditionally been considered less severe than convulsive status epilepticus (CSE) and treated less intensely. In addition, unlike CSE, NCSE often goes unrecognised and is underdiagnosed (3).

Diagnosis requires the presence of behavioural symptoms associated with electroencephalographic (EEG) anomalies. NCSE presents as a persistent confusional state, subtle behavioural or cognitive changes that may last hours or days. Clinical presentation is very inconsistent, varying in intensity from drowsiness and difficulty in concentration to coma. Behavioural disturbances related to these

confusional states are common and may lead, in the absence of EEG evaluation, to misdiagnosis of NCSE as a psychiatric condition (4). The more subtle clinical presentations may not be recognised as NCSE and go untreated if EEG is not performed or patients may be inappropriately treated for another condition such as transitory ischaemic attacks. Moreover, patients in coma may be admitted to intensive care units (ICU) without the associated EEG anomalies being detected.

The ERF Workshop has attempted to provide a classification scheme for NCSE based on age of onset and underlying epilepsy syndromes (2). Whilst this will be invaluable in improving research in NCSE by identifying homogenous patient groups for evaluating pathophysiology, diagnostic procedures and treatments, it is perhaps less useful in routine clinical practice where the underlying epilepsy syndrome may be inadequately characterised. Three phenotypes are commonly seen in practice. These are absence status, complex focal status and NCSE associated with coma. Absence status and focal NCSE can be distinguished easily by EEG, the former being characterised by generalised 2 to 4 Hz spike and wave activity and the latter by more or less focalised discharges generally associated with the temporal or frontal lobe. Absence status is more benign in its clinical presentation and in its prognosis than focal NCSE and is more common in younger patients.

Epidemiology

It is believed that around one-third of all cases of status epilepticus correspond to NCSE (5). The ERF workshop (2) identified and reviewed six epidemiological studies of the incidence of NCSE in a hospital setting (6-11). These have provided incidence rates of between 10 and 40 cases per 100,000 subjects per year, corresponding to between 1000 and 4000 subjects in Belgium per year. However, it is clear that NCSE is under-diagnosed (12) and that a significant proportion of patients with more subtle clinical presentations are not seen systematically in hospitals. NCSE can arise throughout the lifespan, with absence status being particularly frequent in children and teenagers with idiopathic epilepsy syndromes or in young patients with epileptic encephalopathies such as Lennox-Gastaut syndrome, and NCSE associated with coma in the elderly.

Aetiology

The aetiology of NCSE is poorly understood and apparently very heterogeneous. In many cases, NCSE appears to correspond to a conversion of an existing epilepsy syndrome presenting as self-limiting seizures. In the epidemiological studies of NCSE referred to above, between 30% and 50% of subjects with NCSE had a prior history of epilepsy (2). It is probable that poor initial control of seizures favours conversion to NCSE, as is well documented for CSE. A retrospective study (13) of absence status found that the mean age of onset of NCSE was twenty years later than the original diagnosis of absence epilepsy, and followed the development of generalised tonic-clonic seizures.

The aetiology of focal NCSE may involve underlying brain lesions caused by tumours or trauma, as well as cerebrovascular disorders. These can be generally identified by magnetic resonance imaging (MRI). In patients with NCSE associated with coma, the epilepsy may be the cause of the coma in some cases, whereas in others both coma and NCSE can be attributed to another cause, such as hypoxia (14). In some severe epilepsy syndromes such as Lennox Gastaut syndrome, tonic status may appears as coma with subtle clinical signs and fast activities on EEGs. This condition may be precipitated by the introduction of benzodiazepines given for another seizure type. In addition, certain rare genetic conditions or chromosomal anomalies can present as iterative NCSE. An example is ring chromosome 20 syndrome (15).

Apparently successful treatment of CSE (*ie* absence of convulsive activity) may in a minority of cases actually reflect transformation into NCSE (16). For this reason, outcome in CSE needs to be monitored carefully by EEG in patients staying in an abnormal consciousness state.

In some cases, antiepileptic drug treatment itself may induce NCSE. This has been described most convincingly for tiagabine (17-21) and has also been documented for carbamazepine (22). For other antiepileptic drugs, the evidence is anecdotal and the causal relationship between treatment and emergence of NCSE unclear. NCSE may also develop following discontinuation of antiepileptic drugs in general or as part of a benzodiazepine withdrawal syndrome. The latter is particularly frequent in the elderly.

Prognosis

The prognosis of NCSE is traditionally considered to be better (23) than that of CSE. However, prognosis varies according to the type of NCSE and the underlying aetiology (24). In general, absence status appears to be relatively benign. Complex focal NCSE, on the other hand, may result in permanent brain damage or in long-term cognitive impairment, particularly if uncontrolled (5, 25). There have been reports, using serial MRI scans, of localised cerebral oedema associated with focal NCSE which evolves into tissue atrophy (26). However, in such patients, it may not always be clear to what extent NCSE itself, rather than the underlying focal lesion, contributes to the residual neurological deficit (27). Particularly in

children, the peculiar NCSE corresponding to CSWS or ESES may evolve into an epileptic encephalopathy associated with irreversible cognitive deterioration (28). In comatose patients, NCSE, even when successfully treated, is associated with poor prognosis in terms of both neurological outcome and mortality (29-32).

Recommendations

DIAGNOSIS

If patients present with clinical signs that are suggestive of NCSE, an EEG should be performed. These include abrupt, subacute or fluctuating changes in consciousness or behaviour in a patient with known epilepsy or the presence of fluctuating consciousness associated with subtle motor signs. If these are present, diagnosis should be confirmed by EEG. In addition, the presence of remote epilepsy risk factors and of abnormal ocular movements have been shown to be highly sensitive indicators of NCSE (31) and their presence should incite the physician to request an emergency EEG.

EEG evaluation is vital to confirm the diagnosis of NCSE and may also be useful to exclude other potential explanations for the clinical signs, such as metabolic disorders, infections of the nervous system, transient ischaemic events or, in the case of syndromes whose clinical presentation is dominated by behavioural and psychiatric symptoms. Routine EEG should be offered as a screening examination in all neurology departments and should be available around the clock. Currently, this is not the case and the accurate diagnosis of NCSE at night and over weekends is often not possible as qualified staff are not present. This can result in delays in diagnosis and treatment. Minimising the diagnostic delay is an important objective in order to initiate appropriate treatment as rapidly as possible and reduce the risk of possible sequelae. One solution to this would be to train neurology department staff to perform routine EEGs, just as ECG monitoring is offered in internal medicine departments. In addition, resources should be provided to allow their interpretation in a timely fashion. In any case, appropriate coverage of EEG in all neurology departments in Belgium will require further investment in healthcare resources. However, this is a necessity if status epilepticus is to be managed correctly and the long-term consequences of this condition in terms of morbidity and mortality avoided. However, it should be noted that some epileptiform abnormalities can reflect the presence of an acute or subacute lesion and not NCSE. In these cases, effective differential diagnosis has important consequences for treatment, since benzodiazepines will be ineffective.

Even if EEG confirmation of NCSE is not available, intravenous benzodiazepine treatment should be considered as a conservative therapeutic measure if the clinical presentation provides strong reasons to suspect NCSE. In these cases, benzodiazepine administration can also be considered as a diagnostic aid, since disappearance of symptoms or EEG abnormalities following treatment is highly suggestive of NCSE. Special precautions should be taken in some epileptic encephalopathies where benzodiazepines may precipitate a non convulsive tonic status.

A careful medical history should be taken and standard laboratory tests performed to exclude other possible diagnoses. In certain cases, toxicological drug screening may be appropriate if recreational drug use or benzodiazepine use or abuse is suspected.

Neuroimaging is of interest in the case of focal NCSE in order to identify any underlying structural abnormalities. Localised cerebral oedema may also be visible using MRI, but the relevance of this for prognosis and treatment remains unclear. MRI or computerised tomography should be offered to all patients at first presentation of NCSE.

TREATMENT

The treatment of CSWS and ESES will not be discussed. The goals of treatment should be to obtain a cessation of EEG abnormalities in the short term with prevention of breakthrough NCSE in the long-term. There is little evidence from published randomised clinical trials evaluating specific treatments in the management of NCSE, and recommendations are based on clinical experience and extrapolations from clinical reports. Unlike CSE, non-comatose NCSE does not generally need to be treated in the ICU, since it is not life-threatening in the short-term. A neurology ward is a more appropriate context for treatment. Nonetheless, patients who are comatose should be admitted directly to an ICU.

The intensity of treatment and the available treatment options should be selected according to the general condition of the patient, the prognosis, and the suspected aetiology of the NCSE (Fig. 1).

In the case of non-comatose patients, the overall goal should be to identify a treatment regimen that provides good control of epileptiform activity and will be suitable for maintenance therapy. It must be recognised that, in difficult cases, this may take several days. As there is no risk of vital status being compromised in NCSE, this delay is acceptable. For the same reason, intubation or anaesthesia are not appropriate for patients with non-comatose NCSE. The underlying aetiology of the NCSE needs to be identified and treatment adapted accordingly, since the range of antiepileptic drugs available for treatment of focal NCSE is broader than for absence status. Treatment algorithms for absence status and focal NCSE in non-comatose
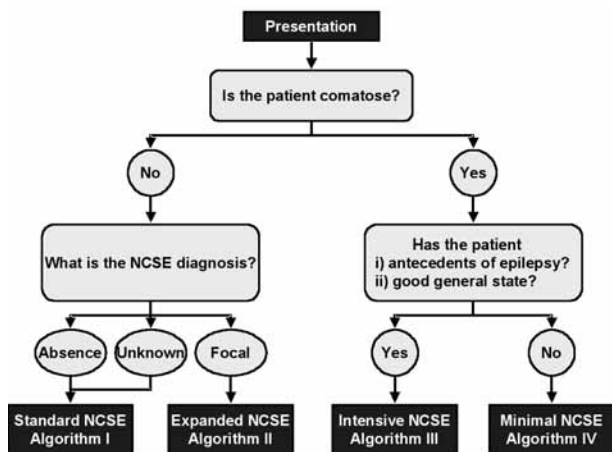
FIG. 1. — Choosing the appropriate treatment algorithm for non-convulsive status epilepticus.
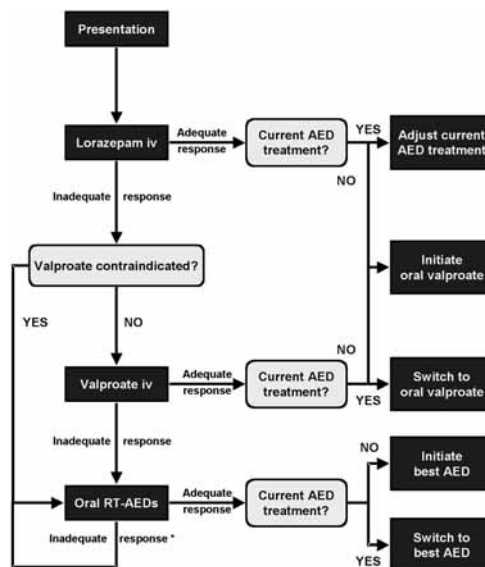

FIG. 2. — Treatment algorithm for non-convulsive absence status epilepticus in non-comatose patients. Black boxes correspond to treatment actions and grey boxes to decision points. The left side of the diagram refers to the acute treatment strategy and the right half to maintenance therapy. The text should be referred to for doses and complete information. AED : antiepileptic drug ; RT : rapidly titrating. *Narrow spectrum AED such as carbamazepine or phenytoin should be avoided.

patients are presented in Figures 2 and 3. If the epilepsy syndrome underlying the NCSE is unknown, the more restricted standard treatment algorithm for absence status should be used as a conservative measure.

In the case of comatose patients with NCSE, the situation is different and treatment will generally be administered in the ICU. Two types of patient should be distinguished. On the one hand, patients with a history of epilepsy and with no or minimal perturbation of major organ function can be identified, for whom NCSE is likely to be responsible for the coma. In these patients, outcome is likely to be good if the NCSE is controlled, leading to rapid resolution of the coma. An intensive treatment regimen is appropriate for these patients, equivalent to that used for CSE (Fig. 4) (1). This involves an accelerated transition through the different treatment levels compared to the standard treatment algorithm for non-comatose NCSE, with recourse to anaesthesia with drugs such as propofol if needed. On the other hand, other patients have major organ failure and the NCSE is likely to be secondary to the events that precipitated the coma. In such patients, use of antiepileptic drugs can be dangerous and intensive treatment may well do more harm than good (12). Overall prognosis is likely to depend more on the resolution of the events that led to the coma in the first place than to successful management of NCSE. For these patients, a minimal treatment regimen restricted to intravenous benzodiazepine administration is appropriate (Fig. 5). It is evident that there will be a spectrum of patients between these two extreme profiles, and clinical judgement should be exercised in identifying the degree of intensity of treatment that has the optimal risk-benefit ratio in individual patients.

The appropriate first-line treatment is intravenous benzodiazepine administration. A long-acting drug should be chosen to maintain control. The most appropriate choice is lorazepam (0.1 mg/kg
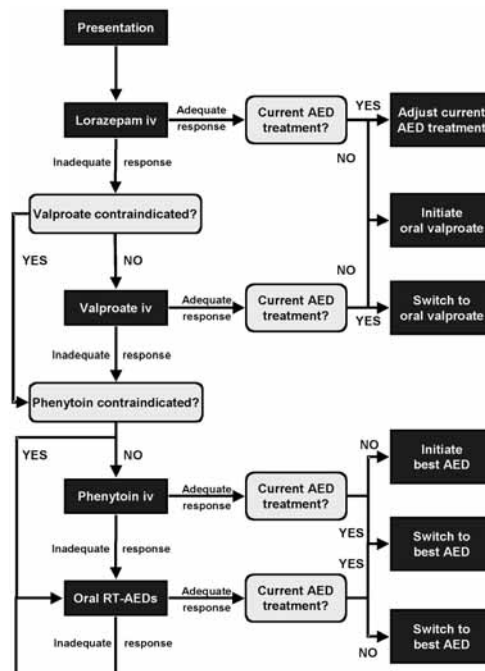

FIG. 3. — Treatment algorithm for non-convulsive focal status epilepticus in non-comatose patients. Black boxes correspond to treatment actions and grey boxes to decision points. The left side of the diagram refers to the acute treatment strategy and the right half to maintenance therapy. The text should be referred to for doses and complete information. AED : antiepileptic drug ; RT : rapidly titrating.

given at a maximal infusion rate of 2 mg/min). Diazepam should be avoided since breakthrough NCSE may occur as the drug redistributes out of
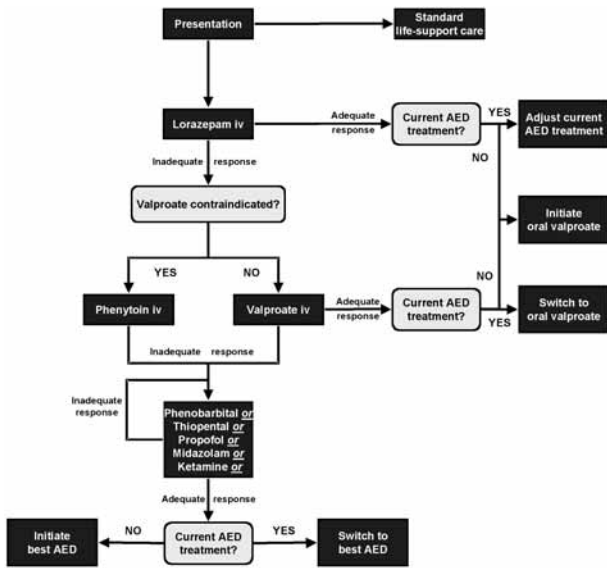
FIG. 4. — Intensive treatment algorithm for non-convulsive status epilepticus in comatose patients with good prognosis. Black boxes correspond to treatment actions and grey boxes to decision points. For further information, see the text. Complete information on this treatment algorithm can be found in the guidelines on convulsive status epilepticus (van Rijckevorsel *et al.*, 2005). AED : antiepileptic drug.
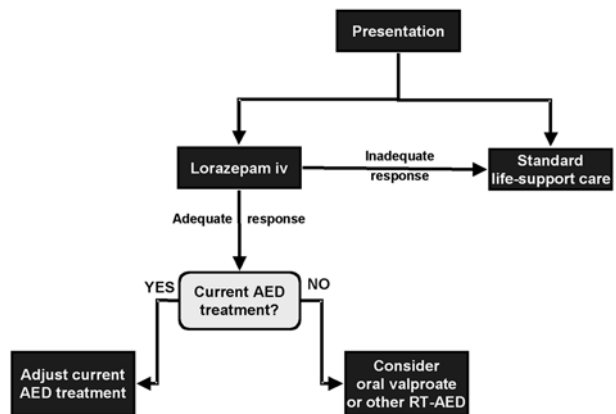

FIG. 5. — Minimal treatment algorithm for non-convulsive status epilepticus in comatose patients with poor prognosis. Black boxes correspond to treatment actions and grey boxes to decision points. The text should be referred to for doses and complete information. AED : antiepileptic drug ; RT : rapidly-titrating.

the nervous system into lipid stores. In general, the response rate to benzodiazepines is lower in NCSE than in CSE and may be less than 50% in patients presenting with comatose NCSE (34).

If benzodiazepines prove unsuccessful in aborting the abnormal EEG activity, then intravenous valproate or phenytoin may be tried, after exclusion of organic causes for the EEG abnormalities. Phenytoin should only be used in focal NCSE as it may cause aggravation of absence status. In absence epilepsy, valproate is the only intravenous treatment option apart from benzodiazepines. The evidence for the efficacy of these drugs is based on published case-reports and our own experience. For example, in a case-series of twelve patients with NCSE (35), nine with complex focal NCSE and three with absence status, who had failed to respond to lorazepam or phenytoin, nine patients responded adequately to intravenous valproate. Similar response rates have been observed in other case series (36-39).

There are no comparative studies available of the relative efficacy of valproate and phenytoin in focal NCSE, but the superior tolerability and ease of use of the former drug (40) would make it the treatment of choice in most cases. In particular, intravenous valproate administration is associated with less hypotension or changes in cardiac rhythm than is intravenous phenytoin. ECG monitoring for patients receiving intravenous phenytoin is recommended, and is mandatory for elderly or otherwise at-risk patients. In contrast, no such ECG monitoring is necessary when using valproate. The use of

intravenous phenytoin may be associated with certain phlebotoxic reactions (precipitation, local injection site reactions due to low pH and purple hand syndrome) and vigilance should be exercised in this respect. These risks may be attenuated by deep-vein infusion, which is, however, more complicated to install. Fosphenytoin, a better tolerated formulation of PHT, is not available in Belgium and has not yet been extensively used in NCSE. Concerning efficacy, two of the case series referred to above have demonstrated responses to valproate in patients who were refractory to phenytoin (37, 41). For these reasons we would recommend valproate as the preferred treatment option in focal NCSE.

Valproate should be given as an initial bolus of 30 mg/kg over 10-15 minutes followed by continuous infusion at a rate of 1 mg/kg/hour until all signs of epileptiform EEG activity have abated. Note that the bolus dose recommended here is higher than that indicated in the summary of product characteristics for valproate. Plasma levels of valproate should be monitored and the infusion rate adjusted if necessary to achieve plasma concentrations of around 80-110 mg%.

Phenytoin can be tried as an alternative option in focal NCSE in patients with contra-indications to valproate or in whom there is a risk of a serious drug interaction with valproate, such as those patients treated with phenobarbital or lamotrigine. In addition, intravenous phenytoin can be tried as a next step in patients who fail to respond adequately to valproate. Case series have reported response rates to phenytoin of 75% to 80% (42, 43). Phenytoin should be administered into a deep vein at an initial dose of 15-20 mg/kg at an infusion rate

of no more than 50 mg/min. It is essential to respect this ceiling as higher infusion rates may be lethal. Top-up doses of 250-300 mg *po* four hours after the initial loading dose or 100 mg *iv* eight hours after can then be given. A total dose of 30 mg/kg/day should not be exceeded. The ECG should be monitored continuously during phenytoin infusion. Plasma levels of phenytoin should be determined episodically and infusion rates adjusted if necessary to achieve a plasma concentration around 20 mg%, with often lower dosages for elderly persons.

For non-comatose patients, if the response to intravenous antiepileptic drugs is inadequate, then addition of a rapidly-titrating oral antiepileptic drug should be attempted. Treatment options for absence status are levetiracetam or topiramate and, in focal NCSE, these two drugs as well as gabapentin or pregabalin. It should be noted that this represents an off-label use of these drugs. Administration through a gastric tube may be appropriate in some cases.

Once the epileptiform anomalies on the EEG have disappeared and a clinical amelioration is noted, treatment should be switched to an appropriate oral maintenance therapy. In previously untreated patients, oral valproate is the preferred treatment option where the patient has responded to intravenous lorazepam or valproate. To maintain protection from recurrence of NCSE in the period before steady-state plasma levels are obtained, concomitant intravenous administration of valproate (1 mg/kg/hour) may be useful during the first twenty-four hours. When patients respond to an antiepileptic drug other than valproate or lorazepam, the most appropriate drug for the seizure type of the individual patients should be chosen for maintenance therapy. In previously-treated patients, adjustment of the previous therapy should be considered or, alternatively, a switch to the drug that successfully resolved the NCSE episode with gradual discontinuation of the original treatment over a few days.

MONITORING

Cerebral electrical activity needs to be followed closely in order to adapt treatment to clinical and EEG response. Ideally, continuous monitoring should be ensured until complete cessation of ictal EEG activity and clinical amelioration is observed. Monitoring of plasma levels of all antiepileptic drugs (except benzodiazepines) administered by the intravenous route should be ensured. In the case of patients treated with intravenous phenytoin, electrocardiographic monitoring will be required. Plasma levels of the new rapidly titrating antiepileptic drugs do not need monitoring, since the dose should be adapted as a function of the clinical response.

SPECIAL POPULATIONS

The recommendations proposed in this consensus paper are useful for most patients. Clinical judgement should, however, be exercised whenever individual patient specificities should be taken into account. In the case of treatment of NCSE in the elderly or in young children, adjustment of the recommended doses of antiepileptic drugs should be performed in accordance with current prescription recommendations in the relevant summaries of product characteristics. It is also important to remember that therapeutic windows are narrower and lower for elderly people, especially for phenytoin.

Conclusions

Although relatively frequent, NCSE is a poorly understood and under-diagnosed condition. However, if recognised, it can be treated successfully in most cases and satisfactory prophylactic antiepileptic therapies put in place, for the greater benefit of the patient's quality of life and to reduce the risk of potentially damaging consequences. NCSE should be suspected whenever cases of fluctuating consciousness or abrupt cognitive or behavioural changes are noted. EEG is critically important for the diagnosis, as it allows the underlying epileptic syndrome to be diagnosed and thus the implementation of the most appropriate strategy. For non-comatose patients, referral to an ICU is most of the time unnecessary. Many non-comatose patients will respond adequately to treatment with valproate, which plays a central role in both the acute treatment and maintenance therapy of NCSE after the acute and diagnostic use of benzodiazepines. For those who do not, time and care should be spent in identifying an appropriate and effective antiepileptic drug regimen without recourse to anaesthesia. EEG plays a vital role in monitoring responses to treatment. For comatose patients, treatment intensity should be graded according to the patients' epilepsy history, general medical state and prognosis. In some patients, intensive remedial measures may allow rapid resolution of the NSCE and interruption of coma, whereas in more vulnerable patients, such intensive treatment may be counterproductive. With the appropriate choice of treatment, as described in these guidelines, most cases of NCSE can be adequately managed.

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