Epidemiology, diagnosis, and management of nonconvulsive status epilepticus

Opening Pandora's box

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Summary

Nonconvulsive status epilepticus (NCSE) is a state of continuous seizure activity for at least 30 minutes, with cognitive or behavioral changes. It may be classified according to EEG evidence of focal or generalized epileptic activity, but may be further categorized by etiology and level of consciousness, both with prognostic weight. There have been several attempts to define the electrographic characteristics of NCSE. Clinical challenges arise from the frequent subtle clinical manifestations, the need for EEG confirmation of ongoing epileptic activity, and physicians' lack of awareness of the possibility of NCSE. This underdiagnosis may have deleterious consequences. This review encompasses epidemiologic, clinical, diagnostic, and prognostic aspects of NCSE in adults, and delineates strategies for management.

Once barely recognized, nonconvulsive status epilepticus (NCSE) steadily became a Pandora's box of unusual clinical features, challenging EEG patterns, and controversial treatments and prognoses. Defined as an ongoing state of seizures, or multiple seizures without convulsions, and without return to baseline for at least 30 minutes,¹ the clinical features of NCSE are highly variable. They include cognitive impairment, speech arrest, subtle facial, trunk, or limb twitches, head or eye deviation, autonomic signs (like unilateral mydriasis, paroxysmal hypertension, or arrhythmias),

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Glossary of terms

ASE = Absence status epilepticus, a subtype of nonconvulsive status epilepticus. Absence status epilepticus is a prolonged, generalized absence seizure, which is defined as lasting >30 minutes but usually lasts for hours or days. The common and major symptom of ASE is impaired cognition, often associated with other clinical manifestations related to the syndrome. Typical findings in EEG are regular and generalized discharges of 1–4 Hz spike or multiple spike-and-slow-wave complexes.

CSE = Convulsive status epilepticus, a subtype of status epilepticus in which excessive and convulsive motor activity is the major symptom.

CPSE = Complex partial status epilepticus, a subtype of nonconvulsive status epilepticus. In complex partial status epilepticus, seizure activity arises in the limbic cortex and can cause unresponsiveness or stupor, automatisms, staring, anxiety, abdominal and vegetative symptoms, or déjà vu. Complex partial status epilepticus can also be of frontal or temporal origin. Symptoms of complex partial status epilepticus of frontal or temporal lobe origin can be very similar.

Epileptic encephalopathy = Severe brain disorder in which the epileptic discharges may contribute to progressive psychomotor dysfunction. The term epileptic encephalopathy encompasses a range of cerebral dysfunctions that are typically related to early age and paroxysmal electrographic brain activity and seizures that are commonly intractable. Cognitive decline and behavioral changes are the main initial and sometimes only manifestation of epileptic discharges. Cognitive, behavioral, and neurologic deficits may be unabating and sometimes ending in early death.

NCSE = Nonconvulsive status epilepticus, a subtype of status epilepticus. It may be classified according to electrographic evidence of focal or generalized cortical seizure activity, but may be further categorized by etiology and level of consciousness, both with prognostic weight. Typical forms of nonconvulsive status epilepticus include typical and atypical absence status epilepticus, simple partial status epilepticus, frontal lobe status epilepticus, and complex partial status epilepticus.

RSE = Refractory status epilepticus. Most studies propose the definition of RSE as a persistent status epilepticus after failure of a first-line (IV benzodiazepines) and one second-line antiepileptic drug (mostly phenytoin, valproate, levetiracetam, or phenobarbital), while others suggest a duration of status epilepticus of >60 minutes.

SE = Status epilepticus, a life-threatening condition in which the brain is in a state of persistent cortical seizure activity. Definitions vary, but traditionally it is defined as one continuous unremitting seizure lasting >30 minutes, or as recurrent seizures without regaining consciousness between the seizures for >30 minutes. Treatment is generally recommended and started after a seizure duration of 5 minutes, as there is some evidence that in this time there can be substantial brain damage and that self-limitation of seizure activity gets unlikely.

SPSE = Simple partial status epilepticus, a subtype of nonconvulsive status epilepticus. Simple partial status epilepticus consists of seizures that are localized to a discrete cortical region and as a consequence do not alter consciousness. Involvement of the cortical motor areas is termed *epilepsia partialis continua*, which typically presents with unilateral, repetitive, and rhythmic twitching of the limb or face.

automatisms, and bizarre behaviors including wandering, hallucinations, fear, and ecstasy. These features can challenge diagnosis, as such symptoms may arise from other conditions. NCSE diagnosis is confirmed by EEG demonstration of ongoing ictal activity.¹

Because the diagnosis depends on the EEG and trained EEG readers, NCSE may be substantially underestimated without the appropriate facilities. Diagnostic acumen for NCSE has been improving, from the increasing use of prolonged video-EEG monitoring, heightened awareness,² and more frequent involvement of neurologists and epileptologists in diagnosis and management.

EPIDEMIOLOGY

Studies of the incidence and prevalence of NCSE are confined to small and mostly single-center investigations,³ mostly without clear distinction between NCSE in the intensive care unit (ICU) vs NCSE in the non-critically ill population. In the United States, the estimated incidence of SE is 15–20/100,000 cases per year⁴—up to 63% of status epilepticus (SE) being NCSE.⁵ In a synopsis of 5 large population-based studies, complex partial SE (CPSE) had the highest incidence (4/100,000 per year).⁴ Of 198 adults admitted to emergency rooms with altered consciousness, no convulsions, and who were referred for an EEG, 37% were found to have NCSE.⁶

Little is known of the burden of NCSE in adults in other parts of the world—especially developing countries. NCSE may be more common in countries with high rates of central nervous infections such as bacterial meningitis, tuberculous meningitis, and HIV-specific central nervous infections (cryptococcal meningitis and toxoplasma encephalitis).

Association with epilepsy

Typical absence status epilepticus (ASE) is the vanguard of epilepsy in ~30% of patients, with recurrence in up to 85%.⁷ NCSE can be preceded by seizures not resulting in SE or by a previous diagnosis of epilepsy. In addition, the incidence of known epilepsy is ~50% of patients with SE.⁵ Formal studies are lacking.

In the intensive care unit

In a prospective study on 236 comatose adult patients without clinical evidence of seizures, 8% met the EEG criteria for NCSE.⁸ A retrospective study in a tertiary care center noted that in almost 50% (52/106) of ICU patients with diagnosed SE, seizure activity was nonconvulsive.³ In a following study, detection of NCSE further increased after implementation of continuous EEG monitoring from 12% (16/129 EEG studies) to 20% (49/249 EEG studies) in patients receiving EEG due to suspected SE.²

Most critically ill patients in ICUs develop SE because of critical illness and SE is the admission diagnosis in a small subset. In a single-center study of patients receiving emergency EEG due to altered mental status, NCSE was reported in 27% (53/198).⁹ In comatose patients with NCSE, 40% had hypoxic-ischemic brain injury and 20% ischemic strokes.⁸ Altered mental status, one of the principal clinical manifestations of NCSE, may be explained by the critical illness itself. Therefore, NCSE can be misdiagnosed as one of several intercurrent illnesses, resulting in delay in diagnosis, which is associated with higher mortality.

RISK FACTORS

Non-neurocritically ill patients

In patients without critical illness, NCSE may arise from an epileptic syndrome, changes in antiepileptic drugs (AEDs), or by interactions that lower AED levels. In patients without epilepsy, however, NCSE may occur from electrolyte disturbances and chronic diseases including slow-growing brain tumors, diffuse cerebral microangiopathy, autoimmune diseases, paraneoplastic syndromes, inherited metabolic disorders, and neurodegenerative disorders. Furthermore, several medications and illicit drugs can cause NCSE (table 1). Interactions between endogenous and exogenous factors in NCSE are illustrated in the figure.

Neurocritically ill patients

Besides the etiologies in non-critically ill patients, NCSE occurs in ICU patients with electrolyte disturbances, acute hormonal disturbances, acute ischemic stroke, intracranial hemorrhage, hypoxic-ischemic encephalopathy after cardiac arrest, and traumatic brain injury.^{9,10}

EEG CRITERIA AND CLASSIFICATIONS OF NCSE

The diagnosis of NCSE depends largely on subjective EEG interpretation without objective numeric criteria for frequency, amplitude, morphology, and evolution of electrographic activity. As the term NCSE includes EEG seizure activity that is prolonged and results in subtle nonconvulsive clinical symptoms, EEG criteria can be categorized as follows¹:

EEG criteria in patients without epileptic encephalopathy

1. Repetitive focal or generalized spikes, polyspike, sharp waves, spike-and-wave, or sharp-and-slow-wave complexes at >2.5 Hz.
2. Above, with discharges <2.5 Hz but with clinical improvement after IV benzodiazepines with increase in EEG reactivity and appearance of EEG background activity.
3. Above, with discharges <2.5 Hz with focal ictal symptoms (e.g., facial twitching, gaze deviation, nystagmus, limb myoclonus).
4. Rhythmic waves at >0.5 Hz (theta-delta) with a) incrementing onset (increase in voltage with increase or decrease in frequency), b) evolution in pattern (increase or decrease in frequency) (>1 Hz) or location, c) decrementing termination (voltage or frequency), or d)

Table 1 Drugs with possible epileptogenic potential

Medication group	Drugs
Drugs mainly acting on the CNS	Antiepileptic drugs (especially large overdoses)
	Benzodiazepines (in the withdrawal phase)
	Phenytoin
	Carbamazepine (may precipitate atypical ASE)
	Tiagabine
	Neuroleptics
	Haloperidol
	Clozapine (olanzapine)
	Phenothiazines
	Antidepressants
	Tricyclic
	Tetracyclic
	Atypical (especially bupropion)
	Lithium
	Opiates (high doses and in the withdrawal phase)
Muscle relaxants	Baclofen
Anesthetics	Meperidine
	Enflurane
Nonsteroidal anti-inflammatory drug	Ketorolac
Antibacterial agents	β -Lactam antibiotics
	Penicillins
	Carbapenems (imipenem, meropenem, doripenem)
	Cephalosporins (especially cefepime)
	Quinolones (especially ciprofloxacin)
	Isoniazid
Antiviral agents	Mefloquine
	Zidovudine
	Acyclovir
	Ganciclovir
	Foscavir
Immunomodulatory drugs	Methotrexate
	Cyclosporine
	Tacrolimus
Oncologic drugs	Ifosfamide
	Chlorambucil
	Busulphan
Asthma drugs	Theophylline
Diet drugs	Phenylpropanolamine

Continued

Table 1 Continued

Medication group	Drugs
Antiarrhythmic drugs	Class Ib (mexiletine, tocainide)
	Class Ic (propafenone)
	Class IV (verapamil)
IV contrast agents	Vascoray
	Iothalamate sodium
	Diatrizoate meglumine
Illicit substances	Alcohol
	Cocaine
	Amphetamines
	γ -Hydroxybutyric acid (only ASE)
	Phencyclidine

Abbreviation: ASE = absence status epilepticus.

post-periodic epileptiform discharges background slowing or attenuation; a–c may be acutely abolished by IV benzodiazepines.

EEG criteria in patients with epileptic encephalopathy

1. Frequent or continuous generalized spike-wave discharges, which show an increase in profusion or frequency when compared to baseline EEG with observable change in clinical state.
2. Improvement of clinical or EEG features with IV benzodiazepines.

Figure Interplay of endogenous and exogenous factors with different contributions to the appearance of nonconvulsive status epilepticus (NCSE)

The diagnosis of NCSE depends largely on subjective EEG interpretation without objective numeric criteria for frequency, amplitude, morphology, and evolution of electrographic activity.

Supplemental Data

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CLINICAL SIGNS AND BEHAVIORAL CORRELATES

We performed a review of the literature for this article regarding symptoms of patients with diagnosed NCSE by using the search engine PubMed (www.ncbi.nlm.nih.gov/pubmed/). Clinical descriptions were identified of 105 patients where EEG patterns were provided. Search terms included “nonconvulsive status epilepticus,” “non-convulsive status epilepticus,” “absence status epilepticus,” and “complex partial status epilepticus.” As only reports with EEG illustrations were selected, there is selection bias. However, most patients had altered mental status (82%). Of those, 49% were confused, 22% were comatose, and 21% were lethargic. Besides altered mental status, speech disturbances (15%), myoclonias (13%), bizarre behavior (11%), anxiety, agitation, or delirium (8%), extrapyramidal signs (7%), and hallucinations (6%) were reported (for references, see appendix e-1). Generalized epileptic activity predominated (64%), while frontal (28%), temporal (20%), central (14%), parietal (9%), and occipital locations (8%) were less frequent.

While NCSE in critically ill patients often consists of secondarily generalized seizure activity and coma, NCSE in non-ICU patients arises from focal epileptic activity with pleomorphic clinical manifestations.

Typical and atypical absence status epilepticus

Typical ASE usually appears in childhood with confusion, psychomotor retardation, perioral, eyelid, and limb myoclonias, sometimes with wandering and a pseudoataxic gait. Verbal skills are relatively preserved. The patient’s awareness of surroundings can lead to misdiagnosis of intoxication, a postictal state, hysterical behavior, or CPSE. Impulsive behavior, agitation, and aggression can emerge. Amnesia varies, with some patients remembering significant events, and maintaining complex activities such as driving, eating, or other tasks. Visceral symptoms include nausea, vomiting, anorexia, and sweating.

Contrasting with ASE, atypical ASE usually occurs with mental retardation and is less often preceded or terminated by tonic-clonic seizures. Interictal fluctuations in responsiveness and attention occur with more pronounced altered consciousness. Ictal and interictal states may merge, and differentiation can be challenging.

Simple partial status epilepticus

Simple partial status epilepticus (SPSE) may produce fear or visceral sensations, adverse eye movements/tonic lateral gaze with nystagmus, prolonged paralysis, or disturbed spatial perception resembling TIAs in awake patients. Occipital simple partial seizures and SPSE produce visual misperception of size and form (metamorphopsia), hallucinations, and reversible blindness. Anterior temporal status may generate depression or behavioral change with suicidal thoughts. Autonomic features (mydriasis, sweating, hypertension, flushing, and arrhythmias) may be prominent with temporal or insular involvement.

Frontal lobe status epilepticus

Patients with frontal lobe SE may have disinhibition, inappropriate smiling or laughter, and confabulation. Others seem indifferent, fearful, angry, irritable, aggressive, or anxious, often with less impairment of consciousness. Frontal NCSE can be categorized into 2 groups: 1) unilateral frontal status with affective disinhibition or indifference, mood disturbances, and subtle cognitive dysfunction, but little or no overt confusion; or 2) bifrontal status with distinct confusion and markedly impaired consciousness.

Temporal complex partial status epilepticus

Patients with temporal CPSE may have variable confusion, agitation, receptive aphasia, and psychosis. Impairment ranges from mild clouding to coma. Patients may reside in a twilight state with partial amnesia, speech arrest, complex automatisms, alimentary automatisms, perseveration, and vocalizations.

Despite the significant semiologic overlap among different syndromes, the combination of symptoms enables distinction among subtypes.

PROGNOSIS

A frequently asked question is “what is the prognosis after NCSE?” Apart from intercurrent medical morbidities, or critical illness, the determinant largely is the underlying cause. Usually, outcome is good in non-ICU patients because patients are not comatose and often respond well to treatment.

In humans, it is difficult to differentiate between brain damage that causes SE and damage resulting from seizures.¹¹ For typical ASE, the morbidity is largely nil. For postanoxic status, it approaches 100%. Even the morbidity in patients with NCSE following CSE (i.e., subtle SE) does not depend on etiology.

Non-neurocritically ill patients

Mortality following NCSE in epilepsy patients with low AED levels was 3%, while it was 27% in patients with NCSE from secondary causes, suggesting that the epileptic activity itself added little morbidity.¹² Patients with idiopathic generalized epilepsy (childhood absence or juvenile myoclonic epilepsy) without additional insults exhibit no MRI evidence of neuronal injury after NCSE. With ASE, there is no subsequent deficit, even after prolonged status. In de novo CPSE from a new insult, there is much speculation on enduring morbidity but with little evidence, or consensus.¹¹ For Lennox-Gastaut syndrome, there are few data on the enduring effects of NCSE, or atypical ASE.

Neurocritically ill patients

Electrographic SE with coma after cardiorespiratory arrest has an almost 100% mortality or nonreturn to consciousness (without therapeutic hypothermia), probably attributable to the anoxia itself. In unconscious survivors of cardiac arrest, seizure activity is not considered the cause of coma or the driver of outcome. Up to one-third of patients have epileptiform discharges during hypothermia or later stages. Patients with preserved brainstem reflexes, normal cortical somatosensory evoked potentials, and EEG background reactivity to noxious stimulation might benefit from antiseizure therapy.

In neurocritically ill patients with metabolic encephalopathy, ischemic strokes, intracranial hemorrhage, or traumatic brain injury,^{9,10} early diagnosis and treatment of ictal activity can reduce morbidity. Patients with intracerebral hemorrhage may have increasing brain edema and midline shift following NCSE, and patients with head trauma and NCSE (compared with controls without NCSE) similarly have a worse outcome.¹⁰ In ischemic stroke, evidence supporting aggressive antiseizure treatment is lacking, although a synergistic effect of injuries from SE and cerebral ischemia may underlie increased mortality in those patients. AEDs and especially IV anesthetic drugs confer some morbidity and mortality. Treatment of NCSE with

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Prospective, randomized trials regarding treatment of NCSE are lacking.

benzodiazepines and anesthetics can cause substantial respiratory suppression, hypotension, prolonged ICU stays, concurrent infection, and death.

MANAGEMENT AND OUTCOME

Therapeutic approaches to NCSE are diverse and controversial, stemming from the different prognoses of the subtypes of NCSE. Prospective, randomized trials regarding treatment of NCSE are lacking. Management decisions are largely based on the individual etiologies underlying the NCSE (e.g., post cardiorespiratory arrest; or multisystem failure in frail ICU patients vs subtherapeutic AED levels in a patient with epilepsy). Table 2 outlines treatment issues in different types of NCSE. As there is lack of evidence for specific treatment regimens in NCSE, and AED therapy is based on case reports, series, and small studies, we suggest treatment strategies reflecting the authors' opinion with corresponding references in the literature (table 2).

First-line treatment

Benzodiazepines are the first-line treatment of SE. A 5-year, randomized, double-blind, multicenter trial of 4 IV regimens (diazepam followed by phenytoin, lorazepam, phenobarbital, and phenytoin) in >500 patients showed that initial treatment with IV lorazepam trended toward being the most effective.¹³ Excellent response rates to first-line benzodiazepines are seen in patients with typical ASE, in case series, and in case reports of patients with simple partial SE. In de novo ASE or CPSE, IV benzodiazepines are effective. Conversely, for atypical ASE or subtle SE, status is refractory to IV benzodiazepines in ~80%–90%.

Second-line treatment

In the randomized, double-blind, multicenter trial noted above with 4 different first-line treatment regimens in a subset of 134 patients with confirmed NCSE following CSE ("subtle SE"), treatment success was 7.7% for phenytoin, 8.3% for diazepam followed by phenytoin, 17.9% for lorazepam, and 24.2% for phenobarbital without significant differences.¹³ Due to the high proportions of first-line treatment failure in patients with "subtle SE," rapid treatment escalation is advocated, but supporting evidence for decreased mortality is lacking. There are no randomized controlled studies on second-line anticonvulsant treatment. Valproic acid, phenytoin, and levetiracetam are the most studied for second-line treatment. Cases with ASE have good responses to first-line benzodiazepines and second-line valproic acid,¹⁴ while atypical ASE and tonic SE show poor or late responses. Phenytoin and valproate are often effective in de novo ASE in elderly, simple partial SE, and nonlimbic complex partial SE when benzodiazepines fail. Limbic CPSE and subtle SE respond poorly. Some case reports and small case series report moderate to excellent response rates with phenytoin, simple partial SE, and nonlimbic complex partial SE—however, phenytoin may worsen de novo ASE, and benzodiazepines worsen tonic status. Levetiracetam is well-tolerated as second-line treatment for SPSE and nonlimbic CPSE.¹⁵ However, further investigations are needed to confirm the assumed treatment efficacy as the patient numbers in this study were low.

Table 2 Suggested treatment approaches for nonconvulsive status epilepticus

		Responses to AEDs				Suggested treatment
NCSE type	Diagnosis	Response	References	Prognosis	Recurrence	
Generalized NCSE						
Typical absence status epilepticus	Frequently missed	Excellent	Case series ¹⁴ and case reports	Excellent	Frequently	PO or IV BZP with supplementation of AED, especially VPA already being used
De novo absence status epilepticus in the elderly	Frequently missed	Good, but sometimes delayed	Case series ^{21,22} and case reports	Excellent	Occasionally	PO or IV BZP with supplementation of AED, especially VPA already being used
Absence status epilepticus with degenerative generalized epilepsies, progressive myoclonic epilepsies	Less frequently missed	Variable	Case series ²³ and case reports	Guarded to fair	Frequent	PO or IV BZP with supplementation of AED, especially VPA already being used
Atypical absence status epilepticus	Less frequently missed	Relatively refractory (in epileptic encephalopathy/ mental retardation)	Case reports	Fair to poor	Frequent	PO or IV BZP; VPA; LEV; TPM; supplementation of prior AED regimen
Simple partial NCSE (nonmotor)	Frequently missed	Excellent	Case series ²⁴ and case reports	Good to excellent (occasionally poor)	Frequent	PO or IV BZP; IV PHT, VPA, or LEV
Complex partial status epilepticus						
Complex partial status epilepticus of frontal lobe origin	Frequently missed	Good, but often delayed	Case reports	Good to excellent	Frequent	PO or IV BZP; IV PHT, VPA, or LEV; supplement prior AED regimen
Complex partial status epilepticus of temporal lobe origin	Less frequently missed	Good, but often delayed	Case reports	Good to excellent	Frequent	PO or IV BZP; IV PHT, VPA, or LEV; supplement prior AED regimen
NCSE presentation by age						
Electrical status epilepticus during slow sleep	Frequently missed	Relatively refractory (in epileptic encephalopathy/ mental retardation)	Case series ²⁵ and case reports	Fair to poor	Frequent	PO or IV BZP; VPA; LEV (polypharmacy should be avoided)
Landau-Kleffner (acquired epileptic aphasia)	Less frequently missed	Relatively refractory (in epileptic encephalopathy/ mental retardation)	Case series ²⁶⁻²⁸ and case reports	Fair to poor	Frequent	PO or IV BZP; VPA; LEV (polypharmacy should be avoided)
Ring-chromosome 20	Frequently missed (time to diagnosis between weeks to 40 years)	May be prolonged	Case series ²⁹ and case reports	Fair to poor	Frequent	IV BZP, but caution: may cause irritation or aggressive behavior

Continued

Table 2 Continued

		Responses to AEDs		Prognosis	Recurrence	Suggested treatment
NCSE type	Diagnosis	Response	References			
Electrographic seizures and coma						
Subtle status epilepticus (usually postconvulsive)	Frequently missed	Poor	Case series ¹³ and case reports	Poor	Few	IV BZP; IV PHT; PRO, MDL, PTB; VPA; LEV; TPM; KTM; LCM; PHB; ketogenic diet
With major CNS damage, often with multiorgan failure (with facial, perioral, or limb myoclonias), but without apparent preceding convulsive status epilepticus	Frequently missed	Poor	Case reports	Poor	Few	IV BZP; IV PHT; PRO, MDL, PTB; VPA; LEV; TPM; KTM; LCM; PHB; ketogenic diet
Abbreviations: AED = antiepileptic drug; BZP = benzodiazepines; KTM = ketamine; LCM = lacosamide; LEV = levetiracetam; MDL = midazolam; NCSE = nonconvulsive status epilepticus; PHB = phenobarbital; PHT = phenytoin; PRO = propofol; PTB = pentobarbital; TPM = topiramate; VPA = valproate.						

Third-line treatment

Third-line drugs are used in refractory SE (RSE). NCSE and focal motor seizures are independent risk factors for RSE, with ongoing seizures in 31% after administration of second-line anticonvulsants. RSE mortality may reach 70%.¹⁶

Third-line drugs such as pentobarbital, midazolam, propofol, and high-dose phenobarbital induce iatrogenic coma, necessitating intubation and mechanical ventilation. Hazards include cardiotoxicity with phenobarbital, severe hypotension with thiopental, or hepatotoxicity and metabolic acidosis with rhabdomyolysis, and cardiac failure in the propofol infusion syndrome. With barbiturates, propofol, or continuous IV midazolam, mortality in RSE may exceed 50%. A systematic review of pentobarbital, midazolam, and propofol for RSE treatment showed pentobarbital to be more effective than midazolam or propofol (8% treatment failure with pentobarbital vs 23% treatment failure with midazolam or propofol; $p < 0.01$).¹⁷ Breakthrough seizures and refractoriness were less frequent with pentobarbital than midazolam or propofol. Severe hypotension was more frequent in patients on pentobarbital than in others, and mortality was 48%, independent of drug or treatment intensity. Outcomes were no different after single or combined regimens.¹⁸

Rescue therapy

There is no standard treatment for super-refractory SE. Ketamine has been successfully used in RSE when midazolam, propofol, and phenobarbital were not, or when midazolam, propofol, and thiopental were insufficient.

In small case series, RSE was broken with lacosamide. Some promising treatment regimens for RSE, such as inhaled anesthetics (isoflurane) and surgery¹⁹ as well as ketogenic diet,²⁰ have recently been reviewed. Choice of third-line drugs and interventions depends on individual considerations.

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