Status Epilepticus: An Evidence-Based Review of Mechanisms, Emergency Care, Rehabilitation, Treatment Lines, and Psychosocial Support for Health Assistants and Social Assistants

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Abstract

Background: Status epilepticus (SE) is a neurological emergency characterized by prolonged seizure activity resulting from failure of normal seizure termination mechanisms. Delayed treatment increases the risk of permanent neuronal injury, systemic complications, cognitive impairment, and mortality. Recent advances have improved understanding of the molecular mechanisms, treatment strategies, and long-term outcomes associated with SE.

Aim: This review aimed to summarize current evidence regarding the pathophysiology, emergency management, treatment algorithms, rehabilitation, and psychosocial support for patients with status epilepticus, with particular emphasis on the roles of health assistants and social assistants in multidisciplinary care.

Methods: An evidence-based narrative review was conducted using findings from experimental studies, prospective clinical investigations, epidemiological research, randomized clinical trials, and contemporary international treatment guidelines. The review integrates current knowledge on neurotransmitter alterations, receptor trafficking, metabolic dysfunction, seizure propagation, pharmacological management, and rehabilitation strategies.

Results: Prolonged seizures produce progressive impairment of GABAergic inhibition, enhanced glutamatergic excitation, disrupted chloride homeostasis, receptor remodeling, and widespread neuronal network activation, leading to pharmacoresistance and neuronal injury. Early benzodiazepine administration remains the cornerstone of treatment, followed by levetiracetam, fosphenytoin, or valproate for established SE. Emerging evidence supports rational polytherapy targeting multiple molecular pathways and highlights potential roles for ketamine, neurosteroids, and metabolic therapies in refractory cases.

Conclusion: Status epilepticus requires immediate evidence-based intervention supported by coordinated multidisciplinary management. Advances in understanding its molecular mechanisms continue to guide development of targeted therapies, while integrating acute treatment with rehabilitation and psychosocial care offers the greatest opportunity to reduce mortality, neurological disability, and long-term disease burden.

Keywords: Status epilepticus, epilepsy, benzodiazepines, refractory status epilepticus, GABA receptors, glutamate, emergency management, rehabilitation, psychosocial support, multidisciplinary care.

Introduction

Status epilepticus (SE) represents one of the most critical neurological emergencies encountered in clinical practice because it is characterized by persistent seizure activity resulting from the breakdown of the physiological mechanisms responsible for terminating seizures or the activation of pathological processes that maintain continuous epileptic discharges. The prolonged nature of seizure activity distinguishes SE from self-limited epileptic seizures and substantially increases the risk of irreversible neurological injury, systemic complications, and mortality if immediate therapeutic intervention is not initiated. The contemporary conceptual framework defines SE as a dynamic pathological process rather than a single event, emphasizing that seizure persistence reflects an imbalance between excitatory and inhibitory neuronal networks. According to the current definition, “Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally prolonged seizures (after time point t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures” [1]. This definition highlights two clinically significant temporal

thresholds. The first threshold, designated as t1, represents the point at which seizure activity is unlikely to terminate spontaneously and therefore requires urgent pharmacological treatment, whereas the second threshold, t2, marks the duration beyond which sustained seizure activity is associated with permanent structural and functional neurological damage. Evidence derived from experimental animal models together with clinical investigations indicates that, for convulsive SE, t1 is approximately five minutes, while t2 is estimated at approximately thirty minutes [1].

Status epilepticus constitutes a significant public health concern because of its relatively frequent occurrence and substantial burden of morbidity and mortality. Epidemiological investigations have demonstrated that the annual incidence of SE ranges between 10 and 41 cases per 100,000 individuals, making it one of the most frequently encountered neurological emergencies requiring immediate medical attention [2, 3]. Despite considerable advances in emergency neurological care, neurocritical care, and antiepileptic pharmacotherapy, mortality remains high, reaching rates of up to 20% in some patient populations [4]. The risk of adverse outcomes is influenced by multiple factors, including patient age, seizure duration, underlying etiology, speed of treatment initiation, and the presence of systemic complications. In adults, SE commonly develops secondary to acute or chronic neurological disorders and systemic medical conditions. Frequent precipitating factors include traumatic and non-traumatic brain injuries, ischemic and hemorrhagic stroke, excessive alcohol consumption or withdrawal, drug intoxication, metabolic disturbances, intracranial hemorrhage, hypoxic brain injury following cardiac arrest, infections affecting the central nervous system, and abrupt discontinuation of antiseizure medications in individuals with preexisting epilepsy [2, 5]. These diverse etiological mechanisms emphasize the importance of comprehensive diagnostic evaluation to identify reversible causes while simultaneously initiating prompt seizure control. The etiological profile of status epilepticus differs considerably in pediatric populations compared with adults. Among children, febrile illnesses represent the most common precipitating factor for SE, particularly during early childhood when the developing brain demonstrates increased susceptibility to prolonged febrile seizures [6]. Importantly, the majority of pediatric patients experiencing febrile status epilepticus are neurologically healthy before their initial episode, suggesting that prolonged febrile seizures frequently occur in children without previous neurological impairment or established epilepsy [7]. This distinction carries important clinical implications because it underscores the need for careful long-term follow-up even in children who appear neurologically normal before the occurrence of SE. Although many pediatric patients recover without immediate neurological deficits, accumulating evidence indicates that prolonged seizure activity during early brain development may have lasting consequences affecting structural brain integrity, cognitive function, and future seizure susceptibility.

Fig. 1: Status Epileptics Guidelines 2026.

Extensive experimental and clinical research has established that prolonged seizure activity can produce selective injury within vulnerable brain regions, particularly the hippocampus, thereby increasing the likelihood of developing temporal lobe epilepsy (TLE) [8-14]. The hippocampus is highly susceptible to excitotoxic neuronal injury because prolonged epileptic discharges promote excessive glutamate release, sustained neuronal depolarization, intracellular calcium accumulation, oxidative stress, inflammatory responses, and disruption of cerebral metabolism. These pathological processes contribute to neuronal loss, synaptic reorganization, and permanent alterations in neuronal circuitry that may facilitate chronic epileptogenesis. Although findings from animal models consistently demonstrated these mechanisms, the long-term consequences of SE in humans remained uncertain for many years due to limited prospective clinical evidence. Substantial clarification regarding the long-term neurological effects of SE emerged from the Febrile Status Epilepticus (FEBSTAT) study, a large prospective multicenter investigation involving children between one month and six years of age who experienced febrile seizures lasting thirty minutes or longer. This landmark study provided compelling evidence that prolonged febrile status epilepticus can produce acute neuronal

injury and contribute to the development of hippocampal sclerosis [15]. The principal objective of the investigation was to determine the relationship between prolonged febrile seizures and the later development of hippocampal sclerosis together with temporal lobe epilepsy. Neuroimaging findings demonstrated that approximately 11.5% of participating children exhibited evidence of acute hippocampal injury on magnetic resonance imaging following febrile SE. Furthermore, comprehensive neuropsychological assessments evaluating cognition, receptive language, and memory revealed that children with febrile status epilepticus were at significantly greater risk of cognitive impairment than children who experienced simple febrile seizures [16]. Longitudinal magnetic resonance imaging performed during extended follow-up demonstrated the subsequent development of hippocampal sclerosis in affected children, reinforcing the association between prolonged febrile seizures and chronic structural brain injury. The study also documented a substantially increased likelihood of seizure recurrence and epilepsy among children with febrile status epilepticus compared with those who experienced uncomplicated febrile seizures [8]. Notably, the cumulative incidence of epilepsy reached approximately 30% over a ten-year follow-up period regardless of the initial MRI findings. Collectively, the findings from the FEBSTAT study provide strong clinical evidence that prolonged status epilepticus can induce hippocampal injury, impair cognitive development, promote hippocampal sclerosis, and significantly increase the long-term risk of temporal lobe epilepsy [8, 15, 16].

From a therapeutic perspective, status epilepticus is classified according to seizure duration and responsiveness to antiseizure medications, allowing clinicians to adopt progressively intensive treatment strategies as pharmacoresistance develops [17]. Early status epilepticus represents the initial phase during which seizures generally remain responsive to benzodiazepines, which constitute the recommended first-line pharmacological therapy because of their rapid enhancement of inhibitory gamma-aminobutyric acid (GABA)-mediated neurotransmission. Failure to achieve seizure termination despite appropriate benzodiazepine administration marks the transition to established status epilepticus, necessitating the administration of second-line antiseizure medications. Persistent seizure activity lasting approximately 60 to 120 minutes despite adequate first-line and second-line therapy defines refractory status epilepticus, a condition associated with markedly increased morbidity, prolonged intensive care admission, and greater risk of permanent neurological injury. The most severe form, super-refractory status epilepticus, refers to seizures that continue for more than twenty-four hours despite treatment with three or more anticonvulsant medications, including general anesthetic agents [17]. This staged classification reflects the progressive evolution of pharmacoresistance that occurs during sustained seizure activity and emphasizes the importance of rapid recognition and aggressive intervention to prevent irreversible neuronal damage, minimize systemic complications, and improve long-term neurological outcomes.

MECHANISMS

Over the past several decades, substantial progress has been achieved in elucidating the molecular and cellular mechanisms responsible for the initiation, maintenance, and progression of status epilepticus (SE). Contemporary research has shifted the conceptual understanding of SE from viewing it solely as prolonged seizure activity to recognizing it as a dynamic process involving continuous alterations in neuronal signaling, receptor trafficking, ion homeostasis, and neural network organization. These discoveries have significantly influenced the revised definition of SE introduced in 2015, which emphasizes that prolonged seizures result from both the failure of physiological mechanisms responsible for seizure termination and the activation of pathological mechanisms that perpetuate seizure activity beyond the critical therapeutic time point (t1) [1, 18-25]. Experimental investigations have demonstrated that sustained seizures progressively remodel inhibitory and excitatory neurotransmission, creating a self-reinforcing cycle that becomes increasingly resistant to conventional antiseizure therapies. The major mechanisms underlying SE include impairment of γ-aminobutyric acid (GABA)-mediated inhibition, enhancement of glutamatergic excitation, disruption of intracellular chloride regulation, receptor trafficking abnormalities, and widespread neuronal synchronization that promotes seizure propagation throughout extensive neural networks.

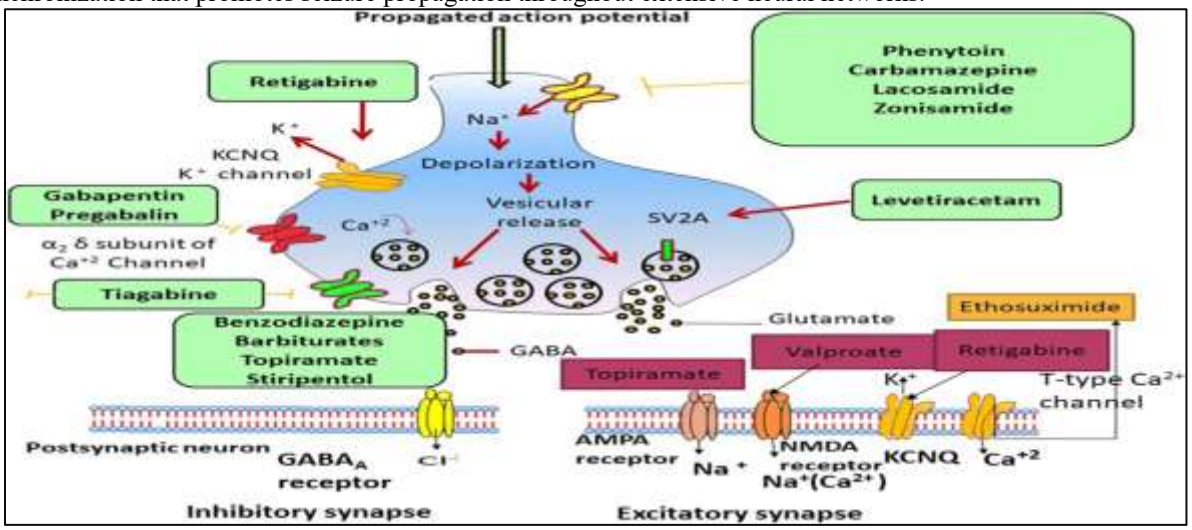

Fig. 2: Status epileptics mechanism.

Impaired GABAergic inhibition

The inhibitory neurotransmitter GABA plays a fundamental role in maintaining the balance between neuronal excitation and inhibition within the central nervous system. Under physiological conditions, activation of GABA-A receptors suppresses neuronal firing by promoting chloride influx, resulting in membrane hyperpolarization and reduced neuronal excitability. During status epilepticus, however, several adaptive and maladaptive molecular alterations progressively weaken this inhibitory system, thereby contributing to persistent seizure activity and pharmacological resistance. Experimental animal studies have consistently demonstrated that prolonged seizures produce significant changes in both the expression and functional activity of GABA-A receptors, together with disturbances in neuronal chloride homeostasis, ultimately impairing the brain's intrinsic capacity to terminate seizures [18-25]. GABA-A receptors are pentameric ligand-gated chloride channels typically composed of two α subunits, two β subunits, and one variable subunit that is usually either γ or δ [26]. The specific composition of these subunits determines receptor localization, physiological function, pharmacological responsiveness, and intracellular trafficking characteristics [27]. Synaptic GABA-A receptors generally contain the γ2 subunit in combination with α and β subunits and mediate rapid inhibitory synaptic transmission through phasic inhibition [28]. These receptors serve as the principal molecular targets of benzodiazepines, which represent the recommended first-line pharmacological treatment for status epilepticus [27, 29]. Benzodiazepines enhance inhibitory neurotransmission by increasing the affinity of GABA-A receptors for endogenous GABA, thereby strengthening inhibitory signaling and facilitating seizure termination. In contrast, receptors containing the δ subunit are predominantly localized within peri-synaptic and extrasynaptic regions where they mediate tonic inhibition, a persistent form of neuronal suppression that regulates baseline neuronal excitability. Unlike γ2-containing receptors, δ-containing receptors exhibit greater sensitivity to endogenous neurosteroids, suggesting an alternative therapeutic pathway for enhancing inhibitory neurotransmission during prolonged seizures. Furthermore, variability among the six α-subunit isoforms substantially influences receptor pharmacology. For instance, receptors incorporating the α4 subunit demonstrate relative resistance to benzodiazepine modulation, illustrating the complexity of GABA-A receptor physiology and its influence on therapeutic responsiveness.

Experimental evidence has shown that benzodiazepines are highly effective when administered during the early stages of status epilepticus but gradually lose efficacy as seizure activity continues and evolves into established SE characterized by continuous electroencephalographic seizure discharges [18]. This progressive pharmacoresistance is largely attributed to activity-dependent internalization of synaptic GABA-A receptors. Investigations involving hippocampal neurons have demonstrated marked reductions in the surface expression of functional synaptic GABA-A receptors during established SE, accompanied by decreased amplitude and frequency of inhibitory synaptic currents as well as diminished whole-cell responses to GABA [18, 19, 22, 24, 30, 31]. Molecular analyses have revealed that prolonged seizure activity promotes receptor dephosphorylation and increases receptor interactions with proteins responsible for endocytosis, thereby accelerating receptor internalization and reducing receptor availability at the neuronal membrane [24, 30, 32]. Because γ2-containing receptors are also the primary targets of benzodiazepines, their loss from the neuronal surface substantially diminishes drug responsiveness and contributes directly to the emergence of benzodiazepine-resistant status epilepticus [18]. Unlike synaptic receptors, extrasynaptic GABA-A receptors containing the δ subunit remain relatively preserved during prolonged seizure activity [19]. This preservation has generated considerable interest in exploiting these receptors as therapeutic targets for established and refractory status epilepticus. Experimental studies have demonstrated that pharmacological agents capable of enhancing extrasynaptic GABAergic inhibition reduce seizure severity in animal models [33]. Preliminary observations from individual clinical cases and small human studies have also suggested potential therapeutic benefits [34-36]. Nevertheless, despite encouraging experimental findings, robust evidence supporting their routine clinical application remains limited, and large-scale randomized clinical trials are still required to establish their efficacy and safety in human patients.

Beyond receptor trafficking abnormalities, disturbances in intracellular chloride regulation further compromise inhibitory neurotransmission during status epilepticus. Under normal physiological conditions, effective GABA-mediated inhibition depends on maintaining low intracellular chloride concentrations, allowing chloride influx to hyperpolarize neurons upon receptor activation. The potassium-chloride cotransporter KCC2 plays a central role in preserving this chloride gradient by continuously extruding intracellular chloride ions [37-39]. Regulation of KCC2 activity depends upon multiple phosphorylation pathways. Phosphorylation of the serine 940 residue by protein kinase C enhances transporter function and stabilizes chloride homeostasis [40, 41]. During status epilepticus, however, dephosphorylation of KCC2 reduces transporter activity, leading to intracellular chloride accumulation and transforming GABA-mediated responses from inhibitory to depolarizing [42]. Consequently, GABA signaling may paradoxically facilitate neuronal excitation rather than suppress it, thereby promoting continued seizure activity. Additional regulatory mechanisms involving the with-no-lysine (WNK) kinase and STE20/SPS1-related proline/alanine-rich kinase (SPAK) further influence KCC2 function. Activation of the WNK-SPAK signaling pathway phosphorylates KCC2 at the threonine 1007 residue, thereby inhibiting transporter activity and further impairing chloride extrusion. Experimental inhibition of WNK kinase prevents KCC2 deactivation during status epilepticus and significantly delays or prevents the development of benzodiazepine resistance [43]. Similarly, pharmacological activation of KCC2 using small-molecule compounds such as compound 350 has demonstrated promising anticonvulsant effects. In experimental brain slice preparations exposed to magnesium-free conditions, compound 350 substantially reduced seizure-like discharges [44]. Moreover, administration of compound 350 together

with diazepam two hours after kainic acid-induced status epilepticus produced marked reductions in electroencephalographic seizure power compared with diazepam treatment alone [44]. These findings suggest that restoration of chloride homeostasis through KCC2 modulation may represent a valuable adjunctive therapeutic strategy capable of enhancing the effectiveness of conventional antiseizure medications during prolonged seizures.

Potentiation of glutamatergic transmission

While impaired inhibitory neurotransmission contributes significantly to seizure persistence, sustained enhancement of excitatory glutamatergic signaling represents an equally critical mechanism responsible for maintaining status epilepticus beyond the therapeutic time point t1 [1]. Seizure initiation and propagation require synchronized neuronal activation, and excessive glutamatergic neurotransmission substantially facilitates this synchronization by increasing neuronal excitability and strengthening excitatory synaptic connectivity. Experimental studies have consistently demonstrated that prolonged seizures induce significant alterations in glutamate receptor expression, phosphorylation, trafficking, and functional activity, thereby amplifying excitatory neurotransmission throughout affected neural networks [20, 21, 23, 45]. Investigations involving hippocampal neurons have revealed increased surface membrane expression of both N-methyl-D-aspartate (NMDA) receptors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors during status epilepticus [20, 21, 23, 45]. Electrophysiological recordings further demonstrate significant increases in both the frequency and amplitude of synaptic currents mediated by these glutamate receptors, reflecting enhanced excitatory synaptic transmission [20, 23, 25, 46]. In addition to increased receptor abundance, prolonged seizures induce alterations in receptor subunit composition that profoundly influence receptor function. One particularly important adaptation involves the internalization of GluA2-containing AMPA receptors accompanied by increased insertion of GluA1-containing receptors into the neuronal membrane [20, 21]. Because GluA2-deficient AMPA receptors exhibit markedly greater calcium permeability, this receptor remodeling substantially increases intracellular calcium influx during excitatory neurotransmission. Excessive intracellular calcium activates numerous destructive signaling pathways, including oxidative stress, mitochondrial dysfunction, protease activation, inflammatory cascades, and apoptotic mechanisms, thereby contributing to glutamate-mediated neurotoxicity, neuronal death, and long-term neurological injury associated with status epilepticus.

Alterations in glutamate receptor composition also modify pharmacological responsiveness. Experimental studies have shown that IEM1460, a voltage-dependent open-channel blocker selective for calcium-permeable AMPA receptors, effectively shortens seizures even when administered after fifteen minutes of continuous seizure activity, suggesting that targeting calcium-permeable AMPA receptors may overcome some limitations associated with delayed benzodiazepine administration [46]. More broadly, numerous investigations have demonstrated that antagonists targeting glutamatergic receptors can terminate seizures even after benzodiazepine resistance has developed, highlighting glutamate receptors as attractive therapeutic targets for refractory status epilepticus [21, 47-51]. Interactions between glutamatergic and GABAergic signaling pathways further amplify seizure persistence. NMDA receptor activation regulates not only AMPA receptor surface expression but also influences the trafficking, clustering, and synaptic stability of GABA-A receptors [20, 52]. Consequently, excessive NMDA receptor activation indirectly weakens inhibitory neurotransmission while simultaneously strengthening excitatory signaling, thereby creating a vicious cycle that favors continued seizure activity and reduces responsiveness to benzodiazepines such as diazepam [53]. Furthermore, calcium influx through NMDA receptors regulates multiple intracellular kinases and phosphatases that control receptor phosphorylation, trafficking, and synaptic localization, reinforcing the extensive molecular remodeling observed during prolonged seizures. Beyond facilitating seizure termination, inhibition of NMDA receptor activity provides important neuroprotective benefits. Experimental studies have demonstrated that NMDA receptor blockade reduces neuronal death, limits hippocampal injury, and decreases epileptogenesis following status epilepticus, thereby reducing the long-term neurological consequences of prolonged seizures [54-57]. These promising findings have stimulated clinical evaluation of ketamine, an NMDA receptor antagonist, as adjunctive therapy for established and refractory status epilepticus. The Ketamine Add-on Therapy for Established Status Epilepticus Treatment Trial (KESETT) seeks to determine whether the therapeutic benefits consistently observed in experimental animal models can be successfully translated into improved clinical outcomes for human patients.

Additional evidence supporting the importance of excitatory neurotransmission arises from studies of organophosphate-induced status epilepticus. Organophosphate compounds, widely recognized as potent acetylcholinesterase inhibitors and chemical warfare agents, produce seizures by causing excessive accumulation of acetylcholine within synaptic clefts [58]. Experimental investigations using paraoxon-induced seizure models have demonstrated that organophosphates activate M1 muscarinic receptors, which subsequently enhance presynaptic glutamatergic neurotransmission and promote sustained seizure activity [59, 60]. These effects are mediated through modulation of M-type potassium channels that regulate neuronal excitability. Pharmacological activation of these channels using flupirtine, administered together with diazepam, has successfully terminated established status epilepticus in experimental animals, illustrating another potential therapeutic strategy targeting the molecular mechanisms responsible for maintaining prolonged seizures [61]. Collectively, these mechanistic insights demonstrate that status epilepticus results from complex interactions among impaired inhibition, enhanced excitation, receptor remodeling, disturbed ion homeostasis, and progressive network synchronization, thereby providing a strong scientific foundation for the development of more effective therapeutic interventions.

Mechanisms Underlying Injury-Induced Status Epilepticus and the Role of Polytherapy

Acute brain injury is a major precipitating factor for status epilepticus (SE), with traumatic brain injury, subarachnoid hemorrhage, and lobar intracerebral hemorrhage representing some of the most important neurological conditions capable of triggering prolonged seizure activity. These forms of injury can give rise to both convulsive and nonconvulsive status epilepticus, each contributing significantly to neurological deterioration and increased mortality [62-65]. Although convulsive seizures are generally recognized promptly because of their overt clinical manifestations, nonconvulsive status epilepticus frequently remains underdiagnosed owing to its subtle or absent motor symptoms. Consequently, delayed diagnosis often postpones therapeutic intervention, allowing seizure activity to persist and increasing the likelihood of irreversible neuronal injury. Clinical investigations have consistently demonstrated that patients with injury-associated nonconvulsive SE experience poorer neurological recovery, prolonged hospitalization, and substantially higher mortality than individuals without persistent seizure activity [66]. These findings underscore the importance of continuous neurological assessment and electroencephalographic monitoring in critically ill patients with acute brain injury. The unfavorable prognosis associated with injury-induced SE is multifactorial and reflects the complex interaction between primary structural damage and secondary pathophysiological processes initiated by persistent seizures. One of the most significant contributors is cerebral edema, which develops following traumatic or hemorrhagic brain injury and leads to progressive increases in intracranial pressure. Elevated intracranial pressure compromises cerebral perfusion, reduces oxygen delivery, and exacerbates ischemic injury, thereby creating an environment that favors ongoing neuronal hyperexcitability and seizure propagation. In parallel, prolonged seizure activity markedly increases cerebral metabolic demand while impairing energy production, resulting in metabolic crises characterized by elevated lactate-to-pyruvate ratios, an established biochemical marker of mitochondrial dysfunction and inadequate oxidative metabolism [67, 68]. The coexistence of cerebral edema, impaired perfusion, metabolic failure, and sustained neuronal excitation establishes a vicious cycle in which each pathological process amplifies the others, ultimately contributing to progressive neurological deterioration and poor clinical outcomes.

Experimental animal models have provided valuable insights into the mechanisms responsible for injury-induced status epilepticus and have reproduced many of the pathological features observed in human patients. Animal studies investigating traumatic brain injury-induced SE have consistently demonstrated high mortality rates together with the frequent occurrence of nonconvulsive seizures, closely resembling the clinical presentation observed in neurocritical care settings [69, 70]. These experimental models have enabled investigators to examine pathological changes that are difficult to study directly in humans during the acute phase of brain injury. One such model involving neocortical injury has demonstrated clear evidence of cerebral edema developing during status epilepticus [69]. Electroencephalographic recordings obtained from these animals reveal a characteristic burst-suppression pattern toward the later stages of seizure activity, accompanied by progressive loss of spontaneous movement, diminished responsiveness, and eventual coma [69]. The emergence of burst suppression reflects profound disruption of cortical electrical activity and indicates severe impairment of neuronal function resulting from sustained seizures and extensive cerebral injury. Breakdown of the blood-brain barrier (BBB) represents another fundamental mechanism contributing to the development of injury-induced status epilepticus. Under physiological conditions, the BBB maintains strict regulation of the exchange of molecules between the systemic circulation and the central nervous system, thereby preserving neuronal homeostasis and protecting neural tissue from circulating inflammatory mediators and plasma proteins. Traumatic injury and intracranial hemorrhage compromise the structural integrity of the BBB, permitting extravasation of blood components into the brain parenchyma [71]. Among the substances entering neural tissue following BBB disruption, thrombin and albumin have received particular attention because of their potent effects on neuronal excitability and seizure generation. Rather than functioning solely as coagulation proteins, these blood-derived molecules actively participate in neuroinflammatory signaling and contribute directly to epileptogenesis following brain injury.

Thrombin has emerged as a particularly important mediator linking vascular injury with seizure development. After entering the brain parenchyma through the disrupted BBB, thrombin activates protease-activated receptors expressed on neurons and glial cells, initiating multiple intracellular signaling pathways that collectively increase neuronal excitability [72-74]. Experimental studies have demonstrated that thrombin enhances persistent sodium currents, thereby facilitating sustained neuronal depolarization and repetitive action potential generation. Simultaneously, thrombin reduces GABAergic inhibitory neurotransmission while potentiating glutamatergic excitatory signaling, producing a profound imbalance between neuronal inhibition and excitation that strongly favors seizure initiation and maintenance [72-74]. These combined effects establish an electrophysiological environment capable of sustaining prolonged seizure activity and may explain the high incidence of SE following traumatic and hemorrhagic brain injuries. Although the mechanisms responsible for post-traumatic epilepsy have been extensively investigated over many years, important knowledge gaps remain regarding the molecular events responsible for acute seizures immediately following brain injury. Most available research has focused on the chronic epileptogenic processes leading to recurrent epilepsy weeks or months after trauma, whereas comparatively fewer studies have examined the cellular and molecular pathways driving early post-injury status epilepticus. Improved understanding of these acute mechanisms is essential because early seizure control may reduce secondary neuronal injury, limit neuroinflammation, preserve neuronal networks, and potentially decrease the subsequent risk of chronic epilepsy. Continued investigation into the interactions among blood-brain barrier dysfunction, inflammatory mediators, ionic disturbances, neurotransmitter imbalance, and metabolic failure will be critical for developing targeted therapeutic interventions

capable of preventing or interrupting injury-induced status epilepticus. Growing understanding of the multiple molecular mechanisms responsible for SE has led to increasing recognition that therapies targeting a single neurotransmitter system may be insufficient once prolonged seizures become established. Status epilepticus involves simultaneous impairment of inhibitory pathways together with progressive enhancement of excitatory neurotransmission, receptor trafficking abnormalities, and intracellular signaling alterations. Consequently, therapeutic strategies that address several pathological mechanisms concurrently have gained considerable attention as potentially more effective approaches for achieving rapid seizure termination [75, 76]. Experimental evidence strongly supports this concept, demonstrating that combination therapies targeting complementary molecular pathways produce greater anticonvulsant efficacy than monotherapy.

Several preclinical investigations have demonstrated the superiority of combination pharmacotherapy in experimental models of established status epilepticus. Administration of diazepam together with ketamine has been shown to terminate prolonged seizures more rapidly than either agent administered alone [50]. This therapeutic synergy likely results from simultaneous enhancement of GABA-mediated inhibition through benzodiazepine activity and suppression of glutamate-mediated excitation through NMDA receptor antagonism. Similar benefits have been observed with combined midazolam and ketamine therapy, which not only effectively terminated seizures but also significantly reduced neuronal injury, subsequent cognitive impairment, and long-term epileptogenesis in experimental animals [77, 78]. These findings indicate that early interruption of multiple pathological pathways may provide both immediate anticonvulsant effects and sustained neuroprotective benefits. Further evidence supporting multidrug therapy has been generated by studies conducted in Wasterlain's laboratory, where combinations including midazolam, ketamine, and valproate, as well as midazolam, fosphenytoin, and valproate, consistently demonstrated greater efficacy than corresponding monotherapies [79]. Importantly, these investigations also revealed that simultaneous administration of combination therapy was superior to sequential administration of the same medications. This observation suggests that delaying treatment of complementary pathological mechanisms allows continued molecular remodeling during ongoing seizure activity, thereby reducing overall therapeutic effectiveness. Simultaneous pharmacological intervention appears to interrupt multiple components of the evolving seizure network before irreversible pharmacoresistance, and neuronal injury become fully established.

Translation of these encouraging experimental findings into clinical practice is currently being evaluated through the Ketamine Add-on Therapy for Established Status Epilepticus Treatment Trial (KESETT; NCT06907173). This multicenter, randomized, blinded clinical trial has been designed to determine whether adjunctive ketamine improves seizure control in patients with benzodiazepine-refractory status epilepticus. Specifically, the study compares the efficacy of adding either 1 mg/kg or 3 mg/kg of ketamine to standard treatment with levetiracetam at a dose of 60 mg/kg against levetiracetam alone. The primary outcome is sustained termination of status epilepticus beginning fifteen minutes after initiation of study drug infusion and maintained for at least sixty minutes without the requirement for additional antiseizure medications. Successful seizure termination is defined by either recovery of consciousness with complete absence of clinically evident seizures after sixty minutes or, in patients undergoing electroencephalographic monitoring, complete absence of electrographic status epilepticus after fifteen minutes despite persistent impairment of consciousness. The results of this trial will provide important clinical evidence regarding whether simultaneous modulation of inhibitory and excitatory neurotransmission through rational polytherapy can improve seizure control and neurological outcomes in patients with established status epilepticus.

Altered Energy Metabolism During Status Epilepticus and Expansion of Neuronal Activity Maps

Status epilepticus (SE) imposes extraordinary metabolic demands on the brain because prolonged and synchronized neuronal firing requires continuous production of large quantities of adenosine triphosphate (ATP). Under physiological conditions, neuronal energy requirements are primarily satisfied through oxidative phosphorylation within mitochondria, a highly efficient process that utilizes glucose and oxygen to generate ATP. During prolonged seizures, however, neuronal energy consumption increases dramatically, often exceeding the capacity of oxidative metabolism to meet cellular demands. As seizure activity persists, cerebral glucose stores become depleted, mitochondrial function becomes increasingly stressed, and alternative metabolic pathways are activated to maintain neuronal survival and sustain electrical activity. These profound metabolic adaptations are now recognized as integral components of the pathophysiology of SE rather than merely secondary consequences of excessive neuronal firing. Experimental investigations have demonstrated that prolonged seizure activity is associated with a marked decline in cerebral glucose availability accompanied by a substantial increase in extracellular lactate concentrations [80, 81]. Traditionally, lactate was regarded primarily as a metabolic byproduct generated through anaerobic glycolysis during conditions of increased energy demand. However, growing evidence has fundamentally altered this perspective by demonstrating that lactate also functions as an important signaling molecule capable of directly regulating neuronal activity. This dual role of lactate highlights the complex relationship between cellular metabolism and neuronal excitability during status epilepticus.

One of the principal mechanisms through which lactate influences neuronal function involves activation of hydroxycarboxylic acid receptor 1 (HCAR1), previously designated as G protein-coupled receptor 81 (GPR81). HCAR1 is widely expressed throughout the brain and serves as a receptor capable of detecting extracellular lactate concentrations [81, 82]. Activation of the lactate-HCAR1 signaling pathway has been shown to suppress glutamatergic neurotransmission, thereby reducing excitatory synaptic activity and potentially limiting seizure propagation [81, 82]. Experimental studies provide compelling support for this protective mechanism. Mice lacking HCAR1 exhibit

prolonged episodes of status epilepticus together with more severe behavioral seizures than wild-type animals, indicating that endogenous lactate signaling contributes significantly to the brain's intrinsic anticonvulsant defenses. These findings suggest that lactate accumulation during prolonged seizures may represent an adaptive response designed to counterbalance excessive neuronal excitation and facilitate seizure termination rather than simply reflecting metabolic failure. The physiological actions of HCAR1 extend beyond modulation of glutamatergic neurotransmission. Experimental evidence indicates that HCAR1 interacts functionally with several additional neurotransmitter systems, including adenosine A1 receptors, GABA-B receptors, and α2A-adrenergic receptors [82]. Each of these receptor systems plays an important role in regulating neuronal excitability and maintaining network stability. Adenosine A1 receptor activation suppresses excitatory neurotransmission and reduces neuronal firing, GABA-B receptors mediate prolonged inhibitory signaling through G protein-coupled mechanisms, and α2A-adrenergic receptors regulate synaptic transmission by reducing neurotransmitter release. Consequently, activation of HCAR1 may exert widespread neuroprotective effects through coordinated modulation of multiple inhibitory signaling pathways. This complex receptor interaction network illustrates how metabolic intermediates can influence neuronal physiology through mechanisms extending well beyond their traditional metabolic functions.

Despite the apparent anticonvulsant properties of lactate signaling, experimental findings also reveal a seemingly paradoxical aspect of cerebral energy metabolism during status epilepticus. Lactate is generated from pyruvate through the catalytic activity of lactate dehydrogenase (LDH), an enzyme that plays a central role in anaerobic glycolysis. Pharmacological inhibition of LDH has been shown to shorten episodes of status epilepticus in experimental models, most likely by depriving hyperactive neurons of an alternative energy source required to sustain continuous electrical activity [80]. These observations illustrate the dual and sometimes opposing roles of lactate during prolonged seizures. On one hand, lactate production provides an essential substrate capable of supporting neuronal energy metabolism when glucose utilization becomes impaired. On the other hand, lactate simultaneously functions as a signaling molecule that suppresses excessive neuronal excitation through HCAR1-mediated pathways. Therefore, modulation of lactate metabolism may influence seizure activity through both bioenergetic and neurotransmitter-mediated mechanisms. This metabolic complexity has substantially expanded current understanding of the relationship between energy metabolism and seizure generation while identifying several potential therapeutic targets for future investigation. Recognition of the importance of cerebral metabolism has also stimulated growing interest in dietary interventions capable of modifying neuronal energy utilization. The ketogenic diet, characterized by high fat content and severe carbohydrate restriction, shifts systemic metabolism from glucose dependence toward ketone body production and has been successfully used for many years in patients with drug-resistant epilepsy. During ketosis, cerebrospinal fluid lactate concentrations increase, reflecting significant alterations in cerebral metabolic pathways [83]. Increasing clinical evidence has demonstrated the feasibility, safety, and tolerability of ketogenic dietary therapy in patients with super-refractory status epilepticus, raising the possibility that metabolic interventions may provide effective adjunctive treatment when conventional pharmacological therapies fail [84]. Although additional randomized clinical studies remain necessary, these encouraging observations suggest that modifying cerebral energy metabolism may represent an important therapeutic strategy for managing prolonged and pharmacoresistant seizures.

Among the ketone bodies generated during ketogenic metabolism, beta-hydroxybutyrate (βHB) has emerged as a particularly important bioactive molecule. Blood concentrations of βHB have been shown to correlate with seizure control in pediatric patients undergoing ketogenic dietary therapy, suggesting that βHB may contribute directly to the anticonvulsant efficacy of the diet rather than serving solely as an alternative metabolic fuel [85]. βHB exerts many of its biological effects through activation of hydroxycarboxylic acid receptor 2 (HCAR2), also known as GPR109A [86]. Experimental investigations in stroke models have demonstrated that the neuroprotective properties of βHB depend upon HCAR2 expression, indicating that receptor-mediated signaling contributes significantly to its beneficial neurological effects [86]. Although the precise role of βHB-HCAR2 signaling during status epilepticus remains incompletely understood, this pathway represents a promising area for future research. Elucidating its contribution to seizure regulation may improve understanding of ketogenic diet efficacy while facilitating development of novel pharmacological therapies that mimic the beneficial effects of ketosis without requiring strict dietary modification. In addition to metabolic alterations, prolonged status epilepticus is characterized by progressive recruitment of neuronal populations throughout the brain, resulting in expansion of seizure activity beyond its site of origin. Understanding the spatial and temporal patterns of neuronal activation during SE is essential for identifying the pathways responsible for seizure propagation, determining the brain regions most vulnerable to injury, and developing targeted interventions capable of interrupting seizure spread before irreversible neuronal damage occurs. Mapping neuronal activity also provides valuable insight into the mechanisms responsible for both the acute manifestations and long-term neurological consequences of status epilepticus.

Historically, techniques such as two-deoxyglucose autoradiography and cFos immunolabeling have been widely employed to identify metabolically active brain regions during prolonged seizures and to characterize the anatomical pathways involved in seizure propagation [87-89]. More recently, advances in transgenic mouse technology have enabled investigators to obtain high-resolution, whole-brain maps of neuronal activation with unprecedented spatial precision. One particularly important methodological advance involves the use of activity reporter targeted recombination in active population (TRAP) mice, which selectively label neurons activated during specific time intervals [90]. Using this technology, investigators have generated comprehensive maps of neuronal activation during hippocampal stimulation-induced status epilepticus [91]. These studies demonstrated that seizure activity initially remains localized within the hippocampus before progressively expanding into interconnected cortical and subcortical

structures through established anatomical projections. As seizures eventually resolve, neuronal activation gradually retreats toward the hippocampus, illustrating the dynamic nature of seizure propagation and resolution [91]. Particular attention has focused on the dentate gyrus because of its critical role in regulating hippocampal excitability. Dentate granule cells receive dense inhibitory synaptic input and normally function as a physiological gate that restricts excessive excitatory transmission into the hippocampus. Breakdown of this dentate gate is believed to permit uncontrolled activation of the trisynaptic entorhinal cortex-hippocampal circuit, thereby facilitating sustained seizure activity [92-94]. Experimental investigations have demonstrated that hippocampal stimulation-induced status epilepticus is associated with early and persistent failure of dentate gate function, whereas other cortical and subcortical regions exhibit peak neuronal activation at different stages during seizure progression [91]. These observations indicate that seizure propagation occurs through highly organized temporal and anatomical patterns rather than diffuse simultaneous activation of the entire brain.

Understanding these propagation pathways has important clinical implications because status epilepticus is associated with substantial mortality, partly resulting from seizure spread into brain regions responsible for autonomic regulation of respiratory and cardiovascular function. Recruitment of these critical brainstems and hypothalamic networks may contribute to respiratory depression, cardiac arrhythmias, hemodynamic instability, and sudden neurological deterioration observed during prolonged seizures. Consequently, identification of the anatomical pathways linking cortical seizure networks with autonomic control centers may facilitate development of targeted interventions capable of reducing seizure-related mortality. Complementary investigations examining neocortical-onset status epilepticus have further clarified the sequential recruitment of neuronal networks during seizure evolution. Using cFos immunolabeling, researchers demonstrated that the early phase of neocortical SE consists of discrete focal seizures arising near the injury site before progressing into continuous bilateral seizure activity [88]. During the initial stages, cFos expression was predominantly confined to the ipsilateral motor cortex, retrosplenial cortex, somatosensory cortex, anterior cingulate cortex, lateral and medial septal nuclei, and amygdala. As status epilepticus progressed, neuronal activation expanded bilaterally to involve the motor and somatosensory cortices together with several subcortical structures, including the hippocampus, amygdala, thalamus, and hypothalamus [88]. These findings strongly suggest that recurrent interactions among cortical and subcortical circuits create self-sustaining excitatory networks capable of maintaining prolonged seizure activity. Recognition of these dynamic network alterations provides valuable insight into the mechanisms responsible for seizure persistence and identifies potential anatomical targets for future therapeutic interventions aimed at limiting seizure propagation and minimizing long-term neurological injury.

Death During Status Epilepticus and the Influence of Gonadal Hormones

Status epilepticus (SE) is associated with substantial morbidity and mortality, making it one of the most life-threatening neurological emergencies encountered in clinical practice. Despite significant advances in emergency medicine, neurocritical care, and antiseizure therapies, mortality rates remain unacceptably high, particularly among adults and older individuals. A prospective population-based investigation conducted in Richmond, Virginia, reported mortality rates of approximately 26% among adults and 3% among children experiencing SE, demonstrating a marked age-related difference in clinical outcomes [2]. Elderly patients represent an especially vulnerable population because they frequently present with multiple comorbid conditions, impaired physiological reserve, and more severe underlying neurological disorders, all of which contribute to increased mortality. Although several factors influence survival, including seizure etiology, duration, treatment delay, and systemic complications, respiratory failure remains one of the leading immediate causes of death, accounting for nearly 30% of fatalities associated with status epilepticus [95]. These observations emphasize that the consequences of SE extend far beyond uncontrolled neuronal activity and frequently involve dysfunction of vital physiological systems responsible for maintaining life. Generalized convulsive status epilepticus exerts profound effects on respiratory physiology. Repeated tonic-clonic seizures significantly disrupt normal respiratory rhythm, impair airway protection, and compromise gas exchange, frequently resulting in hypoxemia, hypercapnia, and respiratory acidosis. Consequently, many patients experiencing prolonged convulsive seizures require endotracheal intubation and mechanical ventilation to maintain adequate oxygenation and ventilation while definitive seizure control is achieved [96-98]. Respiratory dysfunction during SE may result from multiple interacting mechanisms, including seizure-induced depression of central respiratory drive, upper airway obstruction, aspiration, pulmonary edema, and respiratory muscle fatigue. These complications collectively contribute to cerebral hypoxia, exacerbate neuronal injury, and increase the likelihood of fatal outcomes if not recognized and managed promptly. Experimental studies have provided important insights into the temporal relationship between seizure activity and mortality. Investigations conducted in animal models have demonstrated that death frequently occurs within minutes following generalized tonic-clonic seizures during status epilepticus, suggesting that fatal physiological disturbances develop rapidly after severe seizure episodes rather than only after prolonged periods of continuous seizure activity [99]. Moreover, the frequency of severe generalized seizures appears to serve as a reliable predictor of mortality, indicating that repeated recruitment of widespread neuronal networks progressively increases the risk of life-threatening complications [99]. These findings support the concept that seizure severity and propagation patterns may be more important determinants of mortality than seizure duration alone.

The mechanisms responsible for respiratory failure during status epilepticus involve disruption of specialized neuronal circuits located within the brainstem that regulate automatic breathing. The respiratory central pattern generators together with inspiratory and expiratory control centers are primarily situated within the medulla and pons, where they

generate rhythmic respiratory activity independent of conscious control [100]. Although seizures commonly originate within cortical or limbic structures, seizure activity may eventually propagate into these brainstem respiratory networks, thereby disrupting normal respiratory rhythm. An important structure involved in this propagation process appears to be the periaqueductal gray (PAG), a midbrain region that serves as an anatomical and functional interface connecting higher cortical and subcortical regions with brainstem autonomic control centers [101]. Through these extensive neural connections, the PAG may facilitate transmission of seizure activity from forebrain networks into respiratory regulatory circuits, ultimately contributing to respiratory arrest during prolonged seizures. Experimental evidence supports this hypothesis. Studies have demonstrated that repeated generalized tonic-clonic seizures induce episodes of postictal apnea in animal models, with some animals recovering spontaneous respiration while others progress to fatal respiratory arrest [102]. Importantly, repeated severe seizures produce significantly greater neuronal activation within the periaqueductal gray and the dorsal raphe nucleus than a single generalized seizure, suggesting cumulative recruitment of brainstem structures involved in respiratory regulation [102]. These observations indicate that progressive expansion of seizure networks into autonomic control centers may represent a critical mechanism underlying respiratory failure and sudden death during status epilepticus. Understanding the neural pathways responsible for seizure propagation into these life-sustaining brainstem regions may therefore provide opportunities for developing targeted interventions aimed at preventing respiratory collapse and reducing mortality.

Synaptic plasticity within excitatory neuronal circuits also appears to play a pivotal role in determining seizure propagation and its life-threatening consequences. Experimental investigations have shown that seizure-activated hippocampal CA1 neurons exhibit enhanced AMPA receptor-mediated synaptic transmission, reflecting activity-dependent strengthening of excitatory glutamatergic signaling [103]. This form of synaptic plasticity is believed to facilitate progressive expansion of seizure networks throughout interconnected brain regions, thereby sustaining prolonged seizure activity and increasing the likelihood of spreading into autonomic control centers [20]. Consistent with this hypothesis, mice lacking expression of the GluA1 subunit of AMPA receptors develop significantly shorter episodes of status epilepticus, indicating that GluA1-dependent receptor remodeling contributes substantially to seizure persistence. Although detailed mapping of neuronal activation in these genetically modified animals has not yet been completed, it is plausible that reduced GluA1 expression limits seizure propagation by confining neuronal activation to fewer brain regions or by decreasing the intensity of network recruitment. Further support for the importance of AMPA receptor plasticity comes from studies demonstrating that pharmacological inhibition of these receptor changes protects animals from seizure-induced apnea and death [102]. These findings suggest that limiting excitatory synaptic remodeling not only reduces seizure severity but may also interrupt propagation of seizure activity into respiratory control networks. Nevertheless, several important questions remain unanswered. Existing investigations have not specifically examined synaptic plasticity occurring within brainstem respiratory centers themselves. Moreover, studies employing whole-body GluA1 knockout animals or systemic administration of AMPA receptor antagonists cannot distinguish between therapeutic effects occurring within cortical and subcortical seizure networks and those directly affecting brainstem respiratory neurons. Since seizure propagation into brainstem regions may induce similar glutamatergic and GABAergic receptor remodeling, future investigations focusing specifically on receptor plasticity within respiratory control centers will be essential. Likewise, determining whether selective modulation of periaqueductal gray neuronal activity can prevent seizure spread into the brainstem may provide important insights for reducing respiratory complications and mortality associated with status epilepticus.

In addition to neuronal circuitry, biological sex and gonadal hormones significantly influence neuronal excitability, seizure susceptibility, and the molecular mechanisms underlying status epilepticus. Female reproductive hormones, particularly progesterone and estrogen, regulate numerous aspects of neuronal function, including synaptic transmission, receptor expression, and neuronal plasticity [104-109]. These hormonal influences are clinically evident in women with epilepsy who experience cyclical fluctuations in seizure frequency during different phases of the menstrual cycle, a phenomenon known as catamenial epilepsy. Despite extensive investigation of hormonal influences on epilepsy generally, comparatively little is known regarding their effects on susceptibility to status epilepticus or on long-term neurological outcomes following prolonged seizures. Epidemiological studies have consistently reported that the incidence of status epilepticus is higher in men than in women [2, 3, 110-113]. However, whether mortality following SE differs according to sex remains uncertain. Clinical studies have produced conflicting results, with an investigation conducted in Taiwan reporting higher mortality among women [110], whereas two studies from the United States found that female patients experienced lower mortality than males [113, 114]. These discrepancies likely reflect differences in patient populations, underlying etiologies, age distributions, and treatment strategies, emphasizing the need for additional large-scale studies evaluating sex-specific outcomes. Experimental animal models also demonstrate important sex-related differences in seizure susceptibility, although these differences vary depending on the experimental model employed. Male and female mice appear similarly susceptible to pilocarpine-induced status epilepticus and exhibit comparable mortality rates [115]. In contrast, organophosphate-induced seizures show significant sexual dimorphism. Exposure to diisopropylfluorophosphate (DFP) produces more severe seizures in male rats than in females [116, 117], whereas female animals appear particularly susceptible to seizures induced by the organophosphate nerve agents soman and sarin [118-120]. These observations indicate that hormonal influences on seizure susceptibility depend not only on biological sex but also on the specific molecular pathways activated by different seizure-inducing agents.

The reproductive cycle further modifies seizure susceptibility in females. Experimental studies have demonstrated that female rats during the estrus phase exhibit lower susceptibility to status epilepticus than animals studied during

other stages of the estrous cycle, indicating that fluctuating concentrations of ovarian hormones significantly influence neuronal excitability [107]. Additional evidence supporting hormonal regulation comes from studies involving gonadectomized animals. Removal of gonadal hormone production increases susceptibility to kainic acid-induced status epilepticus in both sexes, although this increase appears particularly pronounced in males [121]. These findings suggest that endogenous sex hormones normally exert important modulatory effects on seizure threshold. Progesterone influences seizure activity through multiple distinct mechanisms operating over different time scales. Activation of classical nuclear progesterone receptors alters gene expression, increasing neuronal excitability and enhancing AMPA receptor-mediated glutamatergic neurotransmission within hippocampal and entorhinal cortical neurons [108, 122]. Consistent with these effects, female rats lacking progesterone receptor expression develop shorter episodes of status epilepticus with reduced seizure severity [122]. In contrast, the progesterone metabolite allopregnanolone exerts rapid anticonvulsant actions by directly enhancing GABA-A receptor-mediated inhibition. These effects develop within minutes, whereas genomic actions mediated through nuclear progesterone receptors require several hours because they depend upon altered transcriptional regulation and increased expression of excitatory receptors [108, 122]. This distinction highlights the complexity of progesterone signaling and demonstrates that different progesterone metabolites may exert opposing effects on seizure susceptibility depending on the receptor systems involved. Estrogens also exert complex influences on neuronal excitability. In general, endogenous estrogens synthesized from cholesterol or testosterone display proconvulsant properties, and acute inhibition of estrogen synthesis suppresses status epilepticus [123]. Pharmacological inhibition of aromatase, the enzyme responsible for estrogen production, reduces seizure duration, attenuates behavioral seizure severity, and decreases hippocampal neurodegeneration following status epilepticus in both male and female experimental animals [123, 124]. Nevertheless, estrogen actions appear highly dependent upon dosage, timing, and physiological context. Administration of low-dose estrogen to ovariectomized animals delays the onset of clonic seizures during kainic acid-induced status epilepticus while simultaneously reducing subsequent degeneration of hippocampal CA3 neurons, indicating significant neuroprotective effects under selected conditions [125]. Furthermore, these neuroprotective actions appear to exhibit marked sex specificity. Ovariectomized females receiving estrogen replacement demonstrate reduced hippocampal neurodegeneration after status epilepticus, whereas administration of estradiol to male animals increases neuronal injury [126]. Collectively, these findings demonstrate that gonadal hormones exert complex and sometimes opposing effects on seizure susceptibility, neuronal survival, and long-term neurological outcomes. Continued investigation into hormonal regulation of status epilepticus may facilitate the development of individualized therapeutic strategies that consider biological sex, hormonal status, and endocrine influences when managing this severe neurological emergency.

TREATMENT

The management of status epilepticus (SE) focuses on rapid seizure termination to prevent neuronal injury, systemic complications, and death. Early intervention is essential because treatment effectiveness declines as seizures persist and pharmacoresistance develops. Preventive strategies are particularly valuable for patients with epilepsy who are prone to seizure clusters, which frequently precede SE [127]. Intranasal benzodiazepines have transformed prehospital management by allowing caregivers to administer rescue therapy before emergency medical services arrive. Intranasal diazepam is approved for adults and children older than six years and has demonstrated high bioavailability and seizure control in approximately 87% of treated individuals [128]. Intranasal midazolam is approved for adults and adolescents aged 12 years and older and has been shown to control approximately 61% of seizure clusters for at least six hours [129]. These formulations are simple to administer, avoid delays associated with intravenous access, and reduce emergency department visits and hospital admissions by interrupting seizures before they evolve into status epilepticus. Evidence-based treatment algorithms developed by the American Epilepsy Society divide SE management into stabilization, initial therapy, second-line therapy, and advanced treatment phases according to seizure duration [130]. During the initial phase, prompt administration of an adequate dose of a benzodiazepine is the standard of care. Recommended first-line agents include intramuscular midazolam, intravenous lorazepam, and intravenous diazepam, supported by high-quality clinical trials including the Prehospital Treatment of Refractory Status Epilepticus (PHTRSE), Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART), and Veterans Affairs Cooperative Study [98, 131, 132]. Despite these recommendations, inadequate benzodiazepine dosing remains a major obstacle to successful early treatment. Analysis of more than 9,000 prehospital cases demonstrated that guideline-adherent dosing was uncommon, with only small proportions of patients receiving the recommended dose and route for midazolam, lorazepam, or diazepam [133]. Similar findings emerged from the Established Status Epilepticus Treatment Trial (ESETT), indicating that underdosing is widespread and likely contributes to persistent seizures despite timely drug administration [134, 135]. These findings emphasize that administering the correct dose is as important as minimizing treatment delay.

Approximately 30%–45% of patients remain in status epilepticus despite appropriate benzodiazepine therapy, progressing to established SE that requires second-line antiseizure medications [98, 132, 136]. Recent randomized clinical trials have clarified the optimal management of this stage. The ESETT trial demonstrated that intravenous levetiracetam, fosphenytoin, and valproic acid have comparable efficacy for terminating benzodiazepine-refractory SE [137, 138]. Additional pediatric studies conducted in Australia, New Zealand, and the United Kingdom similarly reported equivalent efficacy and safety between levetiracetam and phenytoin [139, 140]. These findings have established levetiracetam as a practical alternative to phenytoin or fosphenytoin because it is easier to administer, has

fewer adverse effects, and can be infused over approximately five minutes compared with the longer infusion time required for phenytoin. Although fosphenytoin remains an effective treatment, phenytoin formulations are highly alkaline and may cause complications such as purple glove syndrome, characterized by pain, edema, skin discoloration, and tissue necrosis following extravasation. Furthermore, pediatric patients receiving fosphenytoin in ESETT required endotracheal intubation more frequently than those treated with levetiracetam or valproate. Intravenous valproate also represents an effective and generally safe second-line option, although caution is warranted in women of childbearing potential because of the well-established teratogenic risks associated with chronic valproate therapy, while the risk associated with a single emergency dose remains uncertain. Failure of second-line therapy defines refractory status epilepticus, whereas persistence of seizures despite anesthetic therapy for more than 24 hours characterizes super-refractory SE [141]. Management at this stage typically requires admission to an intensive care unit with continuous electroencephalographic monitoring, endotracheal intubation, and administration of anesthetic agents such as midazolam or propofol. Patients are periodically weaned from anesthesia to assess seizure recurrence, and those who continue to seize after repeated attempts at withdrawal are classified as having super-refractory SE. Many affected patients have sustained acute neurological injury or present with new-onset refractory status epilepticus (NORSE), a syndrome associated with particularly poor outcomes [141, 142].

Recent therapeutic research has focused on neurosteroids because experimental studies demonstrate preservation of extrasynaptic GABA-A receptors despite internalization of synaptic receptors during prolonged seizures. This observation suggested that neurosteroids such as allopregnanolone and ganaxolone, which enhance extrasynaptic GABAergic inhibition, might overcome benzodiazepine resistance [35, 143]. Clinical evaluation has produced mixed results. The Brexanolone trial found no significant difference between allopregnanolone and placebo in facilitating successful withdrawal of anesthetic therapy in patients with super-refractory SE [35]. In contrast, the Randomized Therapy in Status Epilepticus (RAISE) trial demonstrated that intravenous ganaxolone achieved significantly higher rates of seizure cessation within 30 minutes compared with placebo, although it did not significantly reduce progression to intravenous anesthesia. These findings suggest potential therapeutic benefit but also indicate that delayed administration after multiple treatment failures may limit efficacy. Earlier use of neurosteroids following benzodiazepine failure may improve outcomes, although this hypothesis requires confirmation in future clinical trials [75]. Additionally, at concentrations required to terminate SE, neurosteroids activate both synaptic and extrasynaptic GABA-A receptors, reducing their pharmacological distinction from conventional anesthetic agents. Reduced neurosteroid sensitivity observed in patients with chronic epilepsy may further limit therapeutic effectiveness, highlighting the need for continued research into more targeted treatment strategies [144-149].

Conclusion

Status epilepticus remains one of the most serious neurological emergencies because prolonged seizure activity rapidly initiates molecular, metabolic, and systemic changes that increase the risk of irreversible brain injury, cognitive impairment, respiratory failure, and death. Contemporary evidence demonstrates that progressive loss of inhibitory GABAergic function, enhancement of glutamatergic neurotransmission, receptor trafficking abnormalities, disrupted chloride regulation, and widespread neuronal network recruitment collectively drive seizure persistence and pharmacoresistance. These mechanistic insights emphasize the importance of rapid recognition and immediate treatment, with prompt administration of appropriately dosed benzodiazepines followed by evidence-based second-line therapies such as levetiracetam, fosphenytoin, or valproate. Management of refractory and super-refractory SE increasingly incorporates combination therapies and emerging treatments targeting multiple pathological pathways. Equally important are early rehabilitation, continuous neurological monitoring, cognitive assessment, psychosocial support, caregiver education, and coordinated multidisciplinary follow-up involving physicians, nurses, health assistants, rehabilitation specialists, and social assistants. This integrated approach not only improves seizure control and functional recovery but also reduces long-term disability, enhances quality of life, and supports successful reintegration of patients into their families and communities. Continued research into targeted therapies and personalized management strategies is expected to further improve outcomes for patients affected by status epilepticus.

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