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Review

Novel drugs and early polypharmacotherapy in status epilepticus

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ABSTRACT

Purpose: Rescue medications for status epilepticus (SE) have a relatively high rate of failure. The purpose of this review is to summarize the evidence for the efficacy of novel drugs and early polypharmacotherapy for SE.
Method: Literature review.
Results: New drugs and treatment strategies aim to target the pathophysiology of SE in order to improve seizure control and outcomes. Changes at the synapse level during SE include a progressive decrease in synaptic $GABA_A$ receptors and increase in synaptic NMDA receptors. These changes tend to promote self-sustaining seizures. Current SE guidelines recommend a rapid stepwise treatment using benzodiazepines in monotherapy as the first-line treatment, targeting $GABA_A$ synaptic receptors. Novel treatment approaches target $GABA_A$ synaptic and extrasynaptic receptors with allopregnanolone, and NMDA receptors with ketamine. Novel rescue treatments used for SE include topiramate, brivaracetam, and perampanel, which are already marketed in epilepsy. Some available drugs not marketed for use in epilepsy have been used in the treatment of SE, and other agents are being studied for this purpose. Early polytherapy, most frequently combining a benzodiazepine with a second-line drug or an NMDA receptor antagonist, might potentially increase seizure control with relatively minor increase in side effects. Although many preclinical studies support novel drugs and early polytherapy in SE, human studies are scarce and inconclusive. Currently, evidence is lacking to recommend specific combinations of these new agents.
Conclusions: Novel drugs and strategies target the underlying pathophysiology of SE with the intent to improve seizure control and outcomes.

1. Introduction

Status epilepticus (SE) is a life-threatening medical emergency. Current guidelines recommend a rapid stepwise treatment first using benzodiazepines in monotherapy, followed by a sequential addition of second-line drugs if SE continues [1]. Approximately one-third of cases of SE remain refractory (RSE) or super-refractory (SRSE) to treatment with benzodiazepines and second-line drugs [2,3]. RSE refers to an ongoing SE despite two appropriately selected and dosed antiepileptic drugs, including one benzodiazepine [4]. SRSE refers to SE that continues 24 h or more after the onset of anesthetic therapy, including recurrences during the reduction or withdrawal of anesthetic agents [5]. Novel rescue treatments and treatment strategies, such as early polytherapy, target the underlying mechanisms of SE with the intention of preventing progression to RSE and the hope of improving neurologic outcomes. In this review article, we summarize the literature on novel drugs and treatment approaches.

2. Pathophysiology of status epilepticus

Advances in pharmacologic approaches to the management of SE may be possible by a greater understanding of the roles of GABA and NMDA receptors. The pathophysiology of SE involves changes in the location and subunit composition of these neurotransmitter receptors. These changes promote self-sustaining seizures and, as SE continues, result in decreasing efficacy of drugs used to treat early stages of SE.

Synaptic $GABA_A$ receptors produce phasic inhibitory currents in response to vesicular release of GABA. These receptors are widespread in the brain, are the target of benzodiazepines, and are internalized during SE decreasing neuronal inhibition [6,7]. In contrast, glutamate

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receptors (mainly NMDA) accumulate in the synaptic membrane during SE, increasing excitation [7–11]. Unlike the widespread expression of synaptic $GABA_A$ receptors, extrasynaptic $GABA_A$ receptors are present only in hippocampus, thalamus, amygdala, hypothalamus, and cerebellum. Activation of these receptors produces non-desensitizing tonic inhibitory currents in response to extracellular GABA. However, these receptors are not targeted by benzodiazepines and are thought to represent a promising novel therapeutic target.

The subunit composition of both GABA and glutamate receptors regulates their localization at the synapse, and their binding properties [12]. The composition of these receptors changes during brain development and in response to seizures [13–25]. In the immature brain and the developing brain exposed to repeated seizures, the composition of $GABA_A$, NMDA and AMPA receptors (increased ratio of non-α1/α1 in $GABA_A$ receptors, GluN2B/GluN2A in NMDA receptors, and GluA1/GluA2 in AMPA receptors) leads to further excitability and promotes self-sustaining seizures [13–25]. In addition, GABAergic neurotransmission is excitatory in the immature brain, since the overexpression of the chlorine NKCC1 transporter promotes intracellular accumulation of chlorine [26]. Collectively, this enhanced neuronal excitability makes the immature brain particularly susceptible to seizures and vulnerable to the development of abnormal neuronal networks during synaptogenesis and cortical formation [27,28].

Disruption of the blood-brain barrier may also contribute to the mechanisms of epileptogenesis [29]. Compromise of the blood-brain barrier, due to prolonged epileptic activity or acute neurologic insults, may allow the invasion of cells and molecules, such as leukocytes and albumin. Albumin can activate astrocytes through calcium signaling [31] and through increase of production of the pro-convulsant cytokine IL-1β [32]. Increase in astrocyte excitability following albumin uptake has been proposed as novel mechanism of epileptogenesis linked to TGFβ-signaling [33]. The invading leukocytes, as well as others cells within the brain (such as activated microglia and astrocytes, neurons, endothelial cells of the blood-brain barrier, and blood-born macrophages) can synthetize and release substances with inflammatory properties leading to an inflammatory cascade -which may decrease the threshold for seizures- in response to multiple factors (such as infections, autoimmunity, and seizures as well) [34]. These inflammatory substances can also actuate as neuromodulators and be involved in seizure generation, epileptogenesis and drug-resistance [35,36]. An altered expression of some transport proteins or drug-metabolizing enzymes at blood-brain barrier may be an additional reason for antiepileptic drug resistance [30,37]. A dysfunctional blood-brain barrier may also enhance or reduce the distribution of antiepileptic drugs into the brain [30].

In conclusion, changes in the location and composition of some neurotransmitter receptors, the blood-brain barrier and neuroinflammation should be considered as potential targets for new antiepileptic drugs, as well as mechanisms of pharmacoresistance to current drugs.

3. Antiepileptic drug options for the treatment of status epilepticus

3.1. Classical drugs

- **Benzodiazepines.** Benzodiazepines are the first-line treatment in current guidelines –although studies did not show a better efficacy stopping seizures compared to 'second-line treatments'- [4,38]. Benzodiazepines are positive allosteric modulators of synaptic $GABA_A$ receptors [4,38–40].
- **Phenytoin (fosphenytoin).** Phenytoin stabilizes the inactive form of neuronal voltage-dependent sodium channels. The main adverse effects are its arrhythmogenicity and drug-drug interactions. Phenytoin has been classically considered the second-line treatment of SE, together with the medications detailed below –published studies show no major differences in effectiveness among second-line drugs- [4,38,40].
- **Phenobarbital.** Phenobarbital is a long-acting barbiturate that enhances GABA-mediated inhibition. This drug may also antagonize AMPA receptors and inhibit neurotransmitter release. Its main adverse effects are potential central nervous system and respiratory depression, as well as drug-drug interactions [40].
- **Valproate.** Valproic acid acts through several mechanisms, including increasing GABA synthesis, inhibiting GABA transaminase, stabilizing voltage-gated sodium channels, and inhibiting T-type calcium channels. Valproate has potential side effects such as pancreatitis, hepatoxicity –mainly in patients with an underlying metabolic disorder-, hyperammonaemic encephalopathy, hematologic disorders, and drug-drug interactions. Carnitine supplementation is frequently given with valproate to reduce its potential toxicity. Valproate can exacerbate some metabolic diseases, and therefore, should be avoided in patients with some known or suspected metabolic disorders [40].
- **Levetiracetam.** Levetiracetam inhibits neurotransmitter release due to its binding to the synaptic vesicle protein 2A (SV2A). Recent studies suggest that this drug may also modulate glutamate receptors (mainly AMPA) [41,42]. The most limiting adverse effect of levetiracetam is agitation or irritability, which is typically not severe, but very common. Levetiracetam is a relatively safe drug without major drug-drug interactions [40].
- **Lacosamide.** Lacosamide enhances the slow inactivation of voltage-dependent sodium channels. This drug is the newest drug among the second-line treatments. Lacosamide could cause cardiac conduction disorders. No drug-drug interactions are known [40].
- **Continuous infusions** of midazolam, thiopental, pentobarbital, or propofol. If SE is ongoing despite first and second-line treatments, an admission to an intensive care unit (ICU) and the administration of sedative drugs by intravenous perfusion is recommended in current guidelines [40].

3.2. Novel drugs

3.2.1. Gender-based differences, allopregnanolone and hormone-based therapy

A neurosteroid is a steroid synthetized within the brain by the glia which has neurological effects [43]. A neuroactive steroid is a steroid with neurological activity, but synthetized outside the central nervous system after conversion of adrenal, gonadal or placental steroids. Neuroactive steroids, derived from progesterone, deoxycorticosterone or testosterone, can cross the blood-brain barrier and modify brain function and structure [43].

Neurosteroids and neuroactive steroids are essential for the sex-dependent differences in brain development, function and structure. The metabolism and levels of neurosteroids or neuroactive steroids, as well as the neuronal receptors and networks affected by them vary with gender. These properties could explain why epilepsy shows gender-based differences regarding incidence, etiology, progression, and responsiveness to treatment [44–46]. For example, men exhibit greater seizure susceptibility in general, while women have greater seizure susceptibility fluctuation due to hormonal variations; women also are more susceptible to some epileptic syndromes which are much more complex and often intractable [47–50].

Neurosteroids –such as allopregnanolone, tetrahydrodeoxycorticosterone (THDOC), and androstanediol- interact with $GABA_A$ receptors. At high concentrations, neurosteroids directly activate these receptors; at low concentrations, they behave as potent positive allosteric agonists. There are two types of $GABA_A$ receptors based on their location: the synaptic and extrasynaptic $GABA_A$ receptors (explained in pathophysiology section). Neurosteroids act on both receptors, showing a greater affinity for the extrasynaptic ones [45,51]. Neurosteroids could be a therapeutic option for SE since they target extrasynaptic $GABA_A$ receptors, which are

not subject to inhibition during SE by other antiepileptic drugs as synaptic $GABA_A$ receptors are.

Allopregnanolone has been studied as potential therapy for the treatment of SE. Many preclinical studies based on animal models of SE show favorable outcomes when using allopregnanolone or other neuroactive steroids [52–61]. A few human studies also show promising results. In 2014, Broomall et al. reported the first use of allopregnanolone in two children with SRSE [62]. Both patients were allopregnanolone responders after the unsuccessful use of other multiple antiepileptic drugs [62]. Similarly, Vaitkevicius et al. reported the effective use of allopregnanolone in two adults with SRSE in 2017 [63]. Initial human studies on neuroactive steroids suggested good efficacy [64]. An open-label multicenter phase1 / phase 2 initially showed evidence to support the use of brexanolone – a proprietary formulation of allopregnanolone– as adjunctive therapy in SRSE [65]. However, the follow-up phase 3 STATUS trial failed to show any difference in the primary outcome (weaning from third line agents) between standard of care and patients treated with brexanolone [66]. Supporting the idea of allopregnanolone as a potential drug for SE, a recent study showed that the levels of this neurosteroid are decreased in cerebrospinal fluid of patients during SE [67]. Other similar neuroactive steroids, such as ganaxolone, are being studied for refractory focal seizures, refractory catamenial epilepsy, infantile spasms, or neonatal seizures [43,68–70].

The role of estrogens in SE remains unclear [71]. In a kainic acid-induced SE mouse model, acute inhibition of estrogen synthesis suppresses SE [72]. However, strogens may have a protecting effect in a pilocarpine-induced temporal lobe epilepsy mouse model [73].

3.2.2. Ketamine and drugs targeting the NMDA receptor

Functional changes in the N-methyl-D-aspartate (NMDA) glutamate receptor are involved in the pathophysiology of SE (see pathophysiology section). Therefore, NMDA receptor antagonists are theoretically a good approach to the treatment of SE [74–76]. Currently, ketamine is the only intravenous NMDA receptor antagonist available in most countries. Ketamine also interacts with other receptors (opioid, monoaminergic, muscarinic and nicotinic receptors), ion channels (L-calcium and sodium channels), and modulates some cytokines (IL-1, 6, 8, 10; TNF-α), which confers some anti-inflammatory properties to this drug [77,78].

Most human studies assessing the efficacy of ketamine in RSE and SRSE are small retrospective series or isolated cases focused on a late use of this drug when the patient is already on polytherapy, which limits any conclusions about efficacy [79–93]. Nevertheless, the use of ketamine for RSE management is increasing given the apparently favorable results in these retrospective series [94]. Ketamine has fewer cardiovascular and respiratory side effects than other anesthetics used for the treatment of SRSE [82]. Traditionally, ketamine has been avoided in patients with increased intracranial pressure due to its potential hypertensive effect, but this association has been called into question [95–97]. Dissociative psychosis could be a potential side effect, but the combination of ketamine with a benzodiazepine mitigates this risk. The first multicenter, randomized, controlled, open-label study assessing the efficacy of ketamine in RSE in children is going on in Italy [98]. An early use of ketamine for the treatment of SE, mainly in combination with other drugs, is being studied in animal models with promising results (see early polytherapy section).

3.2.3. Other drugs

3.2.3.1. Topiramate. Topiramate was successfully used for the treatment of RSE and SRSE in small case series [99–103]. Topiramate acts through multiple mechanisms: enhanced GABA-mediated inhibition, inhibition of sodium currents, enhanced potassium channel conduction, inhibition of L-type calcium channels, decrease of glutamatergic transmission, and inhibition of carbonic anhydrase [40]. The main adverse effect of topiramate is metabolic acidosis. The combination topiramate-valproate should be considered with caution due to the increasing risk of hyperammonaemic encephalopathy. Topiramate is only available enterally, which limits its use in acute situations.

3.2.3.2. Brivaracetam. Brivaracetam has the same mechanism of action as levetiracetam -inhibits neurotransmitter release due to its binding to the synaptic vesicle protein 2A (SV2A)-, but it seems to have higher affinity and, consequently, a faster brain permeability and action onset [104]. Brivaracetam seems to be a safe drug without major drug-drug interactions, and less behavioral side effects compared to levetiracetam. Preclinical studies support the use of brivaracetam in SE, although its use in humans is limited to a small retrospective series of patients with RSE or SRSE with inconclusive results [105–107].

3.2.3.3. Perampanel. Perampanel targets non-NMDA glutamate receptors. It is a selective, non-competitive antagonist of AMPA receptors. As AMPA receptors are involved in the pathophysiology of SE, perampanel may potentially help in SE [108]. Although some preclinical studies support the effectiveness of perampanel [109], this drug has only been analyzed in a few retrospective case reports and series of RSE [110–112] with no conclusive results, possibly due to its late use in the course of treatment of RSE, the use of relatively low doses, and the administration via nasogastric tube.

3.2.3.4. Drugs targeting the immune system. Current immunotherapy in epilepsy is based on immunosuppressants (adrenocorticotropic hormone –ACTH-, corticosteroids, immunoglobulins, plasmapheresis, and monoclonal antibodies), and it is only used in certain conditions (some epileptic types such as infantile spasms, Lennox-Gastaut, severe encephalitis or autoimmune conditions). Novel approaches are focused on targeting key proinflammatory mediators potentially involved in neuroinflammation related to epilepsy [34–36,113,114]:

- Interleukin-1 and its receptor (IL-1, IL-1R)/ High mobility group box 1 (HMGB1) and Toll-like receptor signaling (TLR4). IL-1β, IL-6, TLR4, TNF-α and other cytokines can induce COX-2 through NF-κB.
- Transforming growth factor β signaling (TGF-β), which regulates albumin uptake into astrocytes.
- Cyclooxygenase-2 (COX-2), responsible for the synthesis of prostaglandins [115].
- NOX2 (a NADPH oxidase), which generates reactive oxygen and nitrogen species (ROS/RNS) that can cause oxidative stress and contribute to SE-induced cytokine production [116].
- Others: Tumor necrosis factor alpha (TNF-α), complement system, chemokines.

Van Vliet et al. and Dey et al. have recently published detailed reviews summarizing the seizure mechanisms related to the previous neuroinflammation pathways, as well as a compilation of all the preclinical and clinical studies on anti-inflammatory treatments in epilepsy [35,36]. Regarding SE, an IL-1 receptor antagonist –anakinra- is the first drug targeting the immune system reported as effective in a patient with SRSE secondary to FIRES (febrile infection-related epilepsy syndrome) [117]. A favorable response to IL-1 blockade has also been reported in a few patients with intractable epilepsy [118,119]. In a preclinical study (using kainic acid-induced SE, diazepam-refractory, in a mouse model), the combination of IL-1 receptor antagonist with diazepam terminated established prolonged SE [120]. Furthermore, the administration of IL-1β reduced the efficacy of diazepam, suggesting that IL-1β accumulation may contribute to refractoriness of diazepam in prolonged SE [120].

It is remarkable that many studies about epileptogenesis emphasize the role of the immune system, and many preclinical neuroprotective strategies targeting the immune system show promising results [121–124].

3.2.3.5. Cannabinoids. Recently, there has been an increasing interest for cannabinoids in the field of epilepsy, although there is scarce and contradictory evidence supporting its use [125]. The endogenous cannabinoid system seems to play a role in modulating neuronal excitability, but the exact mechanism remains unclear. Cannabidiol may work through increasing the levels of clobazam and valproate [126,127]. Whether cannabidiol has a direct anticonvulsant effect or simply increases the levels of other antiepileptic drugs is unknown. Some pre-clinical studies suggest that cannabinoids may be useful for the treatment of SE [128–131], but there is no clinical evidence supporting its use beyond increasing the level of other antiepileptic medications. Furthermore, cannabinoids can be epileptogenic depending on the quantity of cannabidiol and Δ9-tetrahydrocannabinol in the drug, and the underlying conditions of the patient [132]. Some studies show SE induced by synthetic cannabinoids [133,134]. The therapeutic use of cannabinoids for SRSE is presented in a single case report without seizure control [135].

3.2.3.6. Bumetanide. Bumetanide is a diuretic that inhibits the Na-K-Cl cotransporter (NKCC1) –a transporter that facilitates the accumulation of chlorine in neurons. Bumetanide has an anticonvulsant effect in kainic acid-induced SE animal models, suggesting a role of chloride homeostasis in seizure progression and development of pharmacoresistant SE [136,137]. NKCC1 cotransporter seems to enhance nonsynaptic epileptiform activity [138]. In some preclinical studies, bumetanide alone was ineffective to terminate SE, but this drug potentiated the anticonvulsant effect of low doses of phenobarbital [139]. Hypoxia-ischemia seems to induce NKCC1 cotransporters in some studies [140]. Based on the preclinical data and the distribution of chloride in the neonatal brain due to the overexpression of NKCC1 transporter (see pathophysiology section), a clinical trial was carried out in Europe to determine the effectiveness of bumetanide as an add-on to phenobarbital for the treatment of seizures in newborns with hypoxic ischemic encephalopathy. This Phase I-II study was stopped early for failure to show efficacy and potential increase in risk of hearing loss in the newborns treated with bumetanide [141]. A similar clinical trial to study bumetanide in newborns with refractory seizures is going on in Boston, US (phase I) [188].

3.2.3.7. Valnoctamide and sec-butylpropylacetamide. Valnoctamide is an amide derivative of valproic acid. This molecule seems to be more potent and to have less adverse effects –no teratogenicity- than valproate in animal models [142–145]. Sec-butylpropylacetamide (SPD) is a homologue of valnoctamide even more potent than valnoctamide in some animal models [146,147]. No human studies are available yet.

3.2.3.8. Others. Other marketed drugs such as lidocaine, felbamate, pregabalin, and gabapentin are used in SE, although the evidence is scarce [148–150]. Many unmarketed drugs for epilepsy treatment are being developed or studied with the goal of improving seizure control (adenosine-releasing silk, AMP-X-0079, 2-deoxy-glucose, huperzine A, imepitoin, minoclycine, NAX 801-2, pitolisant, PRX0023, VLB-01, glibenclamide, P2X7 receptor antagonist) [151–160].

4. Early polytherapy

4.1. Early polytherapy, basic science rationale

SE represents a life-threatening medical emergency, and an early and effective treatment is one of the key determinants associated with a favorable outcome [161]. Our current stepwise guidelines recommend the use of benzodiazepines in monotherapy as the first-line treatment. Nevertheless, published studies show no major differences in efficacy when compared with other antiepileptic drugs [162].

The benzodiazepine resistance in SE is time dependent - greater delay in treatment is associated with increased risk for RSE. This mechanism appears related to changes in neurotransmitters receptors over time. In experimental models, during prolonged seizures -unlike brief seizures-, $GABA_A$ receptors are internalized [6,7,163] while glutamate receptors (mainly NMDA receptors) increase their concentration at the synapse [9]. This decrease in inhibition and increase in excitation promotes that seizures become self-sustaining as their duration increases, which could explain the time-dependent increase in pharmacoresistance [8,164–167]. The benzodiazepine resistance could also be accentuated by other potential mechanisms including changes in other ion channels such as sodium or potassium, cholinergic mechanisms involving acetylcholine, increased expression of drug-metabolizing enzymes at blood-brain barrier, neuroinflammation, neuronal damage, and even by etiology of SE [168].

The pathophysiology of SE suggests the most effective pharmacologic intervention is likely to be early polytherapy –the use of combinations of antiepileptic drugs promptly with the onset of seizures. Despite this, there is still limited evidence on the efficacy of early polytherapy due to the scarcity of clinical studies, although it is remarkable that many preclinical studies support its implementation [169,170].

4.2. Early polytherapy, animal models of SE

Reddy et al. published a detailed review on experimental models of SE [171], which can be classified as follows:

- Electrical models: perforant pathway stimulation and self-sustaining stimulation [172].
- Chemical models: kainic acid, pilocarpine, lithium-pilocarpine, organophosphates, flurothyl, and cobalt-homocysteine thiolactone [173].
- Thermal models: hyperthermia or febrile seizures.
- *In vitro* models: low magnesium in brain slices, high potassium in brain slices, 4-aminopyridine in brain slices, and organotypic slice cultures.
- Refractory models: lithium-pilocarpine [173], kainic acid, and diisopropyl-flurophosphate (DFP).

An isolated animal model cannot recapitulate the diverse etiologies of SE in the human, but the combination of these models could cover the spectrum of human SE and provide an appropriate experimental model.

4.3. Potential appropriate combinations based on animal models

It seems reasonable that early polytherapy is composed of a benzodiazepine and a second-line drug. The following combinations have been tested on animal models (Table 1):

- **Diazepam–phenytoin**. In 1996, Walton and Treiman showed that phenytoin-diazepam combination was more effective than each drug alone in a cobalt - homocysteine thiolactone rat model, without differences in side effects [173]. Interestingly, they observed that the combination was more effective if phenytoin was administered before diazepam [173].
- **Diazepam - phenobarbital ± scopolamine.** In 1996, Walton and Treiman showed that phenobarbital-diazepam combination was more effective than each drug alone in a cobalt - homocysteine thiolactone rat model, without differences in side effects [173]. In 2008, Bankstahl and Löscher showed that a diazepam - phenobarbital combination effectively stopped SE in a lithium-pilocarpine rat model (in a study to test a Pgp inhibitor, a blood-brain barrier protein potentially involved in drug resistance) [37]. In 2015, Löscher pointed out that this combination was not sufficient to prevent SE recurrence. However, when scopolamine (a muscarinic

antagonist) was added to this combination, SE was rapidly terminated without recurrence, suggesting that cholinergic activity may be also involved in SE maintenance [170,174]. Furthermore, scopolamine was related to an antiepileptogenic effect [170].

- **Diazepam - ketamine / midazolam–ketamine**. Niquet et al. showed that midazolam – ketamine combination was more effective than valproate-midazolam combination, valproate-ketamine combination, double-dose of midazolam, ketamine and valproate in monotherapy in a severe lithium-pilocarpine rat model. Furthermore, the midazolam-ketamine combination was related to an antiepileptogenic effect and reduction of acute neuronal injury induced by SE [175]. Martin and Kapur also showed that a diazepam – ketamine combination was more effective than each drug alone in terminating SE in a lithium-pilocarpine rat model [176]. MK-801 (a noncompetitive NMDA receptor antagonist) followed by diazepam, and only in this order, was effective in a lithium - pilocarpine rat model [173]. NPC-17742 (a competitive NMDA receptor antagonist) followed by diazepam was also effective in a cobalt - homocysteine thiolactone rat model [173].
- **Benzodiazepines - ketamine - valproate / benzodiazepines - ketamine–brivaracetam**. A low dose combination of the previous triple therapy (diazepam or midazolam-ketamine-valproate or

Table 1
Compilation of animal and human studies about early polytherapy in status epilepticus.

Study	Subjects	Compared alternatives	Outcome	Results	EP
Animal models					
Walton and Treiman, 1996 [173].	C-HT rat model	DZP-PHT vs PHT-DZP vs DZP vs PHT vs placebo	Efficacy (ranking based on type, number and duration of seizures during 2h observation, elapsed time 2nd drug, EEG severity).	PHT-DZP the most effective (followed by DZP-PHT, monotherapy no effective). No differences in side effects.	+
Walton and Treiman, 1996 [173].	C-HT rat model	PB-DZP vs PB vs DZP vs placebo (DZP-PB no tested, since no differences depending on the order were observed previously)	Efficacy (ranking based on type, number and duration of seizures during 2h observation, elapsed time 2nd drug, EEG severity).	PB-DZP the most effective (monotherapy no effective). No differences in side effects.	+
Bankstahl and Löscher, 2008 [37]. Löscher, 2015 [170].	L-P rat model (adult female SD and Wistar rats)	PB-DZP vs PB-PHT/FPHT vs each drug alone (x2) ---------- DZP-PB-scopolamine vs DZP-PB vs DZP	Efficacy for SE termination –in a study to test Pgp inhibitor- (absence of all clinical and EEG evidence of seizure activity within 30 min after drug). ---------- Efficacy to stop SE (without recurrence within first 24h).	PB-DZP the most effective (no efficacy in other groups). ---------- DZP-PB-scopolamine the most effective. Antiepileptogenic effect of scopolamine.	+
Niquet et al., 2016 [175].	Severe L-P rat model (adult SD rats)	MDZ – KET vs VPA-MDZ vs VPA-KET vs MDZ (x2) vs KET (x2) vs VPA (x2)	Reducing several parameters of SE severity, based on EEG (EEG power integral, spikes, seizures, amplitude, spike/burst activity, etc; 24h EEG).	MDZ-KET the most effective, with less brain injury, less epileptogenesis, and less Morris water maze deficits.	+
Martin and Kapur, 2008 [176].	L-P rat model (adult male SD rats)	DZP-KET vs DZP vs KET vs placebo	SE termination measured by EEG activity for at least 5h (termination when EEG turned to baseline or irregular spikes without recurrence of seizures) and behavior observation.	DZP-KET the most effective.	+
Walton and Treiman, 1996 [173].	L-P rat model (adult male SD rats)	MK-801*- DZP vs MK-801 vs DZP vs DZP- MK-801	Survival to SE, with maintained normal EEG and without side effects (normal behavior next day and normal overnight weight gain).	MK-801 –DZP: the most effective, no side effects. MK-801 alone: side effects. DZP alone: no survival.	+
Walton and Treiman, 1996 [173].	C-HT rat model	NPC-17742*- DZP vs NPC-17742 vs DZP vs placebo	Efficacy (ranking based on type, number and duration of seizures during 2h observation, elapsed time 2nd drug, EEG severity).	NPC-17742 –DZP the most effective. No differences in side effects.	+
Wasterlain et al., 2011 [179]. Niquet et al., 2017 [177].	Severe L-P rat model (male Wistar rat)	DZP-KET-VPA (low dose) vs each drug alone (even high doses)	Reducing several parameters of SE severity, based on EEG (EEG power integral, Hjorth function, spikes, seizures –number, cumulative time, composite-, amplitude, time to normality, SE duration, etc). 24h EEG.	Triple therapy more effective than monotherapy without adding side effects.	+

(continued on next page)

Table 1 (*continued*)

Niquet et al., 2017 [178].	Severe L-P rat model (male SD rats)	MDZ-KET-VPA (low dose) vs monotherapy or dual therapy combinations (higher-doses) vs MDZ-FPHT-VPA	Reducing several parameters of SE severity, based on EEG (EEG power integral, Hjorth function, spikes, seizures –number, cumulative time, composite-, amplitude, time to normality, SE duration, etc). 24h EEG.	MDZ-KET-VPA the most effective, with less brain injury and spatial memory deficits. No differences in side effects. Simultaneous triple therapy more efficient than sequential triple therapy.	+
Wasterlain et al., 2011 [179].	Severe L-P rat model	DZP-KET-BRV (low dose) vs DZP (even high dose)	Reducing several parameters of SE severity, based on EEG (EEG power integral, Hjorth function, spikes, seizures –number, cumulative time, composite-, amplitude, time to normality, status duration, etc). 24h EEG.	Triple therapy more effective and less toxic than monotherapy with DZP.	+
Mazarati et al., 2004 [180].	PPS (male Wistar rats)	DZP-LEV (low dose) vs DZP vs LEV vs placebo	Efficacy based on EEG (quantification of seizures and spikes). 24h EEG.	Dual therapy better than monotherapy. LEV better than DZP. No differences in side effects.	+
Kaminski et al., 2009 [181].	(Review) LEV enhances multiple AEDs -mainly with GABAergics or anti-glutamatergics- in different animal models, without increasing side effects.				+
Niquet et al., 2017 [107].	PPS (male Wistar rats)	DZP-BRV (low dose) vs DZP vs BRV vs placebo	Efficacy based on EEG (quantification of seizures and spikes). Acute and long-term (24h, 6-8w, 12m).	Dual therapy more effective. No differences in side effects.	+
Hanada et al., 2014 [109].	L-P rat model (male SD rats)	DZP-PER vs DZP vs PER vs GYKI52466	SE termination based on EEG (spike-free at 30 min drug) and behavior observation.	Dual therapy more effective than DZP; as affective as PER, but with less dose dual therapy.	+
Xu et al., 2016 [120].	KA rat model (WT C57BL/6 mice)	DZP – IL-1Ra vs DZP vs IL-1Ra vs placebo	SE termination based on EEG (ictal discharge). 1h EEG.	Combination more effective.	+
Human studies					
Treiman et al., 1998 [162].	384 adults overt GCSE, 134 subtle GCSE.	LZP vs PB vs PHT vs DZP-PHT. Randomized, double-blind.	Seizure activity termination (based on EEG and motor activity after 20 min, and no recurrence in 40 min).	No differences among arms (intention-to-treat analysis).	-
Sreenath et al., 2010 [183].	178 children GCSE.	LZP vs DZP-PHT. Randomized.	Seizure activity termination (based on clinical activity after 10 min, and no recurrence in 18h).	No differences.	-
Aranda et al., 2010 [184].	Adults. 101 episodes GCSE.	Observational study (evaluation professional practice).	Use of AEDs. Seizure activity termination (after 20 min, and no recurrence in 1h, based on clinical activity +/-EEG).	DZP/CZP-FPHT better than BZD alone.	+
Navarro et al., 2016 [185].	203 adults GCSE.	CZP-LEV vs CZP-placebo. Randomized, double-blind, phase 3.	Seizure activity termination (after 15 min).	Stop. No differences.	-

EP: early polytherapy. +: in favor of early polytherapy. -: inconclusive for early polytherapy. C-HT: cobalt-homocysteine thiolactone. L-P : lithium-pilocarpine. PPS: perforant pathway stimulation. KA: kainic acid. SD: Sprague-Dawley. WT: wild-type. DZP: diazepam. PB: phenobarbital. PHT: phenytoin. MDZ: midazolam. KET: ketamine. BRV: brivaracetam. LEV: levetiracetam. VPA: valproate. PER: perampanel. IL-1Ra: IL-1 receptor antagonist. LZP: lorazepam. BZD: benzodiazepine. CZP: clonazepam. MK-801: noncompetitive NMDA receptor antagonist. NPC-17742: competitive NMDA receptor antagonist. SE: status epilepticus. AEDs: antiepileptic drugs. GYKI52466: AMPA antagonist. GCSE: generalized convulsive status epilepticus. FPHT: fosphenytoin. h: hour. w: week. m: month. min: minutes. vs: versus. x2: double dose.

diazepam-ketamine-brivaracetam) was more effective than each drug in monotherapy and some dual therapies tested, showing synergistic properties [177–179], on a severe cholinergic rat model. In addition, a lower dose of drug was effective in combination treatments, without additional side effects. Midazolam-ketamine-valproate was also more effective than midazolam-fosphenytoin-valproate, highlighting the importance of blocking the NMDA receptor in SE [178].

- **Diazepam - levetiracetam / diazepam–brivaracetam**. The diazepam-levetiracetam combination was more effective than diazepam alone for the termination of SE, even when both drugs were given in lower dosage than usual [180]. Levetiracetam seems to be a universal enhancer of many antiepileptic drugs –mainly with GABAergics or anti-glutamatergics-, without showing differences in

side effects, and independently of the animal model used [181]. The diazepam-brivaracetam combination has also been tested showing better results in combination, and with lower doses as well [107]. Both studies were carried out in a rat model of perforant pathway stimulation of self-sustaining SE.

- **Diazepam–perampanel.** The diazepam – perampanel combination was more effective than diazepam alone, and as effective as perampanel but with less dose in dual therapy, in a lithium-pilocarpine SE rat model [109].
- **Diazepam- IL-1 receptor antagonist.** This combination was more effective than each drug alone in a kainic acid-induced SE rat model [120].
- **Atropine - ketamine.** Although this review is focused on early polytherapy, it is remarkable that this combination proved effective in the delayed treatment of SE in a soman-poisoned male guinea pig model [182].

4.4. Early polytherapy, human studies

There are few human studies on early polytherapy. In 1998, the 'Veterans Affairs Status Epilepticus Cooperative Study Group' carried out a randomized, double blind, multicenter trial comparing four treatments for generalized convulsive SE in adults: lorazepam, phenobarbital, phenytoin, or a combination of diazepam and phenytoin [162]. The trial showed no differences among the arms in an intention-to-treat analysis. As initial treatment for overt generalized convulsive SE, lorazepam was superior to phenytoin. In 2010, another randomized controlled trial in children compared lorazepam to diazepam-phenytoin combination, showing that lorazepam was as efficacious and safe as the combination diazepam-phenytoin, and therefore, the use of lorazepam as a single drug was recommended [183]. In 2010, a cohort study focused on the evaluation of professional practice in front of generalized convulsive SE in adults showed that the combination of diazepam or clonazepam with fosphenytoin allowed a high rate of SE termination than benzodiazepines alone, emphasizing that it could be related to an early use of long-acting antiepileptic drugs other than benzodiazepines [184]. Recently, a randomized, double-blind, phase 3 trial comparing prehospital treatment with levetiracetam plus clonazepam to placebo plus clonazepam in SE found no statistical differences [185]. Nevertheless, levetiracetam does not specifically target the underlying and evolving pathophysiology of SE, although a few recent studies suggest this drug may also modulate glutamate receptors [41,42]. Although this review article is focused on early polytherapy, it is worthy of note that later combinations in RSE or SRSE, such as midazolam-pentobarbital or propofol-ketamine, have shown favorable outcomes [186,187].

4.5. Early polytherapy, potential risks

The main potential risk of early polytherapy would be the increase of potential adverse effects. Early polytherapy implies an additional risk of side effects with no benefit for patients who would have responded to monotherapy with benzodiazepines. However, approximately one third of patients require a second-line antiepileptic drug. For this reason, non-life-threatening side effects may be less important than the potential to have a rapid and effective termination of seizures. Furthermore, many studies suggest that when using early polytherapy less dose of each drug is needed, decreasing potential side effects. The risk-benefit ratio of early polytherapy in SE seems rational, but the literature on this topic is still limited.

5. Future directions

Novel drugs targeting the underlying pathophysiology of SE are developed with the goal of improving seizure control and outcomes. SE can be caused by a wide variety of etiologies including infections, metabolic disorders, genetic conditions, and immunologic processes, as well as responses to drugs may be modified by genetic polymorphisms. Accordingly, even for drugs which target the underlying pathophysiology of SE, there are major challenges in translating their efficacy in pre-clinical studies into efficacy in clinical trials. These characteristics of children with SE are a major challenge to any attempt to establish a single common, well-defined and effective treatment algorithm for SE, RSE or SRSE, since treatment should ideally be adapted to each specific etiology and patient characteristics. Future directions should be addressed to identify and treat mechanisms which are common to multiple etiologies and which incorporate understanding of the pharmacogenetic factors that regulate drug target engagement and pharmacokinetics. Many fundamental questions regarding the treatment of SE and progression to SRSE remain unanswered, including: what is the best drug combination?; what is the optimal sequence of drug administration?; what is the most effective time-lag between each drug?; what is the best dosage when combining drugs?; are there any modifiable mechanisms of pharmacoresistance?; which patients will become refractory to benzodiazepines?; what is the exact role of the blood-brain barrier and the immune system in SE?; should new drugs target receptors involved in seizure termination?; what are the mechanisms underlying seizure termination? A better understanding of these questions could help to achieve a more successful treatment algorithm for SE, and therefore, to reduce the percentage of treatment failure and adverse drug effects.

6. Conclusions

A better understanding of the pathophysiology of SE allows for developing well-targeted novel drugs and improving the management approach of this condition. The early combination of antiepileptic drugs targeting different receptors involved in the dynamic synaptic changes during SE may potentially improve seizure control and outcomes.

Ethics

This study complied with biomedical research ethical standards.

Funding

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Declaration of interest

Mark Wainwright is a member of the Clinical Advisory Board for Sage Therapeutics.

The authors report no potential conflicts of interest.

Contributors

Marta Amengual-Gual participated in drafting and revising the manuscript for content, including medical writing for content, in study concept and design, and study supervision.

Iván Sánchez Fernández participated in revising the manuscript for content, including medical writing for content, in study concept and design, and study supervision or coordination.

Mark Wainwright participated in medical writing for content, in study concept and design, and study supervision or coordination.

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