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Why won't it stop? The dynamics of benzodiazepine resistance in status epilepticus

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Abstract | Status epilepticus is a life-threatening neurological emergency that affects both adults and children. Approximately 36% of episodes of status epilepticus do not respond to the current preferred first-line treatment, benzodiazepines. The proportion of episodes that are refractory to benzodiazepines is higher in low-income and middle-income countries (LMICs) than in high-income countries (HICs). Evidence suggests that longer episodes of status epilepticus alter brain physiology, thereby contributing to the emergence of benzodiazepine resistance. Such changes include alterations in $GABA_A$ receptor function and in the transmembrane gradient for chloride, both of which erode the ability of benzodiazepines to enhance inhibitory synaptic signalling. Often, current management guidelines for status epilepticus do not account for these duration-related changes in pathophysiology, which might differentially impact individuals in LMICs, where the average time taken to reach medical attention is longer than in HICs. In this Perspective article, we aim to combine clinical insights and the latest evidence from basic science to inspire a new, context-specific approach to efficiently managing status epilepticus.

Epilepsy is a condition characterized by recurrent spontaneous seizures that affects more than 50 million people worldwide, the majority of whom live in low-income and middle-income countries (LMICs)[1]. Seizures are associated with multiple risks, including fractures, bruising, head trauma and premature mortality. One of the most important causes of epilepsy-related mortality is status epilepticus, a state of unrelenting seizure activity that persists for more than 5 min[2]. Status epilepticus is a neurological emergency, and prompt action to stop these prolonged seizures can reduce both morbidity and mortality.

Benzodiazepines can terminate seizures by enhancing $GABA_A$ receptor ($GABA_AR$)-mediated signalling and are the preferred first-line management of status epilepticus in both adults and children[3–7]. These medications are easy to administer, cost-effective and often successful in terminating status epilepticus, especially if used early after the onset of seizure activity[5,7]. Failure of two adequate doses of appropriate benzodiazepines to terminate status epilepticus necessitates the use of second-line anti-seizure medications such as fosphenytoin, phenytoin, phenobarbital, levetiracetam or valproate[8–11]. In some cases of status epilepticus, third-line management is required with anaesthetics such as thiopentone and propofol[12,13]. Therefore, benzodiazepine-resistant status epilepticus requires additional medications, sophisticated drug administration (including syringe drivers for infusions and non-glucose prepared solutions for drugs such as phenytoin) and access to intensive care services that can provide close monitoring and invasive ventilation[5,14]. These interventions might not always be readily accessible, particularly to those living in resource-limited countries[15–19].

In this Review, we explore benzodiazepine-resistant status epilepticus from both scientific and clinical perspectives. We focus on convulsive status epilepticus (CSE) in adults and children. We briefly discuss implications for other less common forms of status epilepticus, namely non-convulsive status epilepticus (NCSE) and neonatal status epilepticus. We review the current clinical literature to assess global trends in benzodiazepine-resistant CSE and discuss experimental research that describes the possible pathophysiology underlying benzodiazepine resistance. Here, we focus on the $GABA_AR$ — the principal target of benzodiazepines — and explore the multiple seizure-induced changes that alter the sensitivity of $GABA_AR$ to benzodiazepines during the evolution of ongoing seizure activity. Last, we highlight unanswered questions and suggest possible considerations for improved treatment strategies based on the latest experimental studies and multicentre randomized clinical trials.

Global relevance

Making an accurate estimate of the current epidemiology of status epilepticus is difficult. Substantial variation in study designs and the introduction of new diagnostic criteria in 2015 impede the comparison of results across studies[20–23]. Data are often not stratified across age groups or across different types of status epilepticus, which makes it challenging to estimate the burden of CSE in adults and children. However, on the basis of available data, the global annual incidence of status epilepticus has been reported to range from 14 to 35 per 100,000 children[24–26] and from 5 to 36 per 100,000 adults[27–29]. As CSE is the most common presentation of status epilepticus, these figures might more closely reflect the incidence of CSE. A bimodal age distribution seems to be present, with the peak incidence in early childhood (within the first decade of life) and a progressive rise of status epilepticus incidence in older individuals from the sixth decade of life onwards[27,30]. Febrile illness in children and stroke in adults are the most common causes of CSE[27,28,30–32]. In LMICs, infectious causes such as cerebral malaria can add to the prevalence and severity of CSE[25,33,34].

The management of CSE has been of global academic interest for many decades,

Table 1 | **Studies showing resistance to first-line treatment with benzodiazepine monotherapy in convulsive status epilepticus**

Study	Country	Episodes[a]	Cohort	BZP-R (%)	Latency (min)
Low-income and middle-income countries[b]					
Das et al. (2020)[189]	India	94	Paediatric	89	>60
Burman et al. (2019)[8]	South Africa	144	Paediatric	48	31–60
Hassan et al. (2016)[190]	India	84	Mixed	78	>60
Thakker and Shanbag (2013)[191]	India	50	Paediatric	54	31–60
Misra et al. (2012)[192]	India	79	Adult	24	10–30
Gathwala et al. (2012)[193]	India	120	Paediatric	14	Not reported
Arya et al. (2011)[194]	India	141	Paediatric	18	Not reported
Chen et al. (2011)[195]	China	121	Adult	38	31–60
Skinner et al. (2010)[196]	Honduras	31	Adult	65	>60
Amare et al. (2008)[197]	Ethiopia	119	Adult	63	31–60
Mpimbaza et al. (2008)[198]	Uganda	330	Paediatric	37	>60
Ahmad et al. (2006)[199]	Malawi	80	Paediatric	25	>60
Fişgin et al. (2002)[200]	Turkey	45	Paediatric	42	>60
Tabarki et al. (2001)[201]	Tunisia	139	Paediatric	45	>60
High-income countries[b]					
Theusinger et al.[c] (2019)[202]	Switzerland	126	Adult	28	10–30
Theusinger et al.[c] (2019)[202]	Switzerland	39	Paediatric	3	10–30
Kay et al. (2019)[203]	Germany	42	Adult	28	31–60
Navarro et al. (2016)[204]	France	68	Adult	16	>60
Chamberlain et al. (2014)[205]	USA	273	Paediatric	15	Not reported
Silbergleit et al. (2012)[40]	USA	509	Mixed	43	Not reported
Chin et al. (2008)[206]	UK	240	Paediatric	35	31–60
McIntyre et al. (2005)[207]	UK	219	Paediatric	58	31–60
Qureshi et al. (2002)[208]	UK	48	Paediatric	25	31–60
Mayer et al. (2002)[209]	USA	83	Adult	69	>60
Alldredge et al. (2001)[41]	USA	134	Adult	49	31–60
Lahat et al. (2000)[210]	Israel	44	Paediatric	5	10–30
Coeytaux et al. (2000)[211]	Switzerland	172	Mixed	50	31–60
Scott et al. (1999)[212]	UK	42	Mixed	33	31–60
Treiman et al. (1998)[152]	USA	384	Adult	35	31–60
Chamberlain et al. (1997)[213]	USA	24	Paediatric	8	31–60
Appletan et al. (1995)[214]	UK	86	Paediatric	21	31–60
Remy et al. (1992)[215]	France	39	Adult	28	Not reported

BZP-R, percentage of episodes that were resistant to first-line benzodiazepine treatment. [a]Episodes refers to the number of episodes of convulsive status epilepticus analysed in each study (sample size). [b]Income classification based on gross national income per capita (in US dollars) from the latest ratings[216]. [c]Data from same study across different age groups.

with the use and efficacy of benzodiazepines being among the most studied topics[13]. A number of studies have given either direct or indirect indication of the efficacy of first-line benzodiazepine monotherapy (TABLE 1). By taking an average of the results of these studies, we conclude that, globally, resistance to first-line treatment with benzodiazepines occurs in approximately 36% of patients with CSE (FIG. 1a). The average reported rate of resistance was higher in studies from LMICs than in studies from high-income countries (HICs). Supplementary Fig. 1 shows socioeconomic and temporal differences in benzodiazepine-resistant CSE stratified according to age group and number of study participants. The rate of benzodiazepine resistance reported varied from 3% to 89%; this large range is likely to reflect the substantial heterogeneity in study designs and protocols used. Our estimate of benzodiazepine resistance is more than double that quoted previously by Treiman[35] in 1990 (~17% versus ~36%). This difference is likely to result from the large number of studies that have been conducted since that original report, including the availability of more data from LMICs.

The duration of CSE is an important indicator of whether a patient will respond to a first-line benzodiazepine. A relationship between treatment latency — defined as the time between the start of CSE and administration of a first dose of benzodiazepine — and benzodiazepine resistance has been demonstrated in prospective observational studies conducted in both LMICs[36] and HICs[14,37]. Obtaining an accurate estimate of CSE latency is often difficult as it relies on a witness being present when the CSE started or for care providers to record the time of seizure onset[23]. Furthermore, the initial presentation might represent intermittent seizures that only later progress into CSE, with the two being viewed as separate phenomena. By synthesizing the results of the studies in TABLE 1 that report CSE latency, we observed that, as the duration of CSE increases, so too does resistance to first-line benzodiazepines (FIG. 1b). We noted that in studies reporting CSE episodes exceeding 60 min, the resistance to first-line benzodiazepines is as high as 89%. One can postulate that this phenomenon is likely to be more pronounced in resource-limited countries owing to challenges in health-care access. This hypothesis is supported by our observation that the majority of studies from LMICs reported episodes of CSE that were longer than 60 min in duration (FIG. 1c). Another important variable might be the underlying aetiology of CSE, but the current body of literature does not separate cases of benzodiazepine-resistant status epilepticus by cause of seizures. To gain an understanding of how underlying aetiology contributes to benzodiazepine resistance, further studies are required.

Dosing for first-line benzodiazepine trials was not consistent across studies. Theoretically, to be deemed benzodiazepine-resistant, a patient in status epilepticus should show no response to a benzodiazepine even if given the maximum safe total dose.

In reality, however, many patients do not receive adequate doses of benzodiazepines, with this being particularly pertinent for out-of-hospital status epilepticus[38,39]. This under-dosing might be attributed to the administration route — for example, benzodiazepines are less well absorbed when administered rectally than when administered intravenously[40,41] — or to clinicians choosing to administer an alternative anti-seizure medication instead of a second dose of benzodiazepine. Moreover, some care providers are overly cautious in administering the recommended doses of benzodiazepines out of concern about causing respiratory depression that would necessitate ventilatory support[38]. However, the likelihood of this adverse event occurring has yet to be sufficiently studied in the context of CSE.

Taken together, the evidence discussed above indicates that duration of status epilepticus is an important determinant of response to benzodiazepines[14,42]. This relationship indicates that the pathophysiology of status epilepticus involves adaptive changes in the brain that occur during the evolution of status epilepticus, ultimately affecting the efficacy of benzodiazepines. Understanding the sequence in which such changes occur might provide important insights into how the treatment of status epilepticus can be optimized. As benzodiazepines target the $GABA_AR$, consideration of the structure and function of this chloride (Cl^-)-permeable ionotropic receptor is important for understanding how benzodiazepine resistance might emerge in status epilepticus.

The $GABA_A$ receptor

The $GABA_AR$ is a pentameric, ligand-activated, ionotropic receptor that is formed by different permutations of five constitutive subunits[43,44]. The receptor is largely, but not exclusively, expressed on the postsynaptic membrane of neurons. The different subunits are separated into classes (α, β, γ, δ, ε, π, θ) according to their amino acid composition. Some of these subunits can be further classified into different isoforms ($\alpha_{1–6}$, $\beta_{1–3}$, $\gamma_{1–3}$). The combination of subunit classes and isoforms ultimately determines the biophysical properties of the channel, including its localization, ligand binding and conductance[44]. The most common arrangement of the $GABA_AR$ in the rodent and human brain is two α_1-subunits, two β_2-subunits and a γ_2-subunit[45–54]. It is evident from studies in rodent brain tissue that receptors of this composition are associated with phasic inhibition and are located at most GABAergic synapses (FIG. 2).

The γ-subunit is considered to be crucial for the clustering of $GABA_AR$ at synapses[55]. Consistent with this view, in rodents in vitro studies have found that $GABA_ARs$ in which the γ-subunit has been replaced by a δ-subunit are present at extrasynaptic sites[56,57]. $GABA_ARs$ are activated by the neurotransmitter GABA, which binds between the α- and β-subunits[58,59]. This binding induces a conformational change in the pentameric channel to make it selectively permeable to Cl^- and, to a much lesser extent, bicarbonate (HCO_3^-)[60–62]. Cl^- flux predominates and, under physiological conditions, the transmembrane electrochemical gradient favours Cl^- movement into the cell. $GABA_AR$ activation therefore typically causes a net inward movement of negative charge and membrane hyperpolarization (FIG. 2a). This process underlies the 'classic' inhibitory action of $GABA_ARs$.

The function of the $GABA_AR$ can be enhanced or attenuated using various pharmacological manipulations[43,44,63]. Benzodiazepines, formed from the union of the benzene and diazepine chemical rings[64], are a class of synthetic $GABA_AR$-positive allosteric modulators that can enhance $GABA_AR$ conductance. By enhancing GABAergic signalling, benzodiazepines typically have anti-seizure, sedative, hypnotic and anxiolytic properties. The effect of benzodiazepines on the brain is determined by the different subunit configurations of the $GABA_AR$ that are present and their relative distribution throughout the CNS[52]. Furthermore, the different benzodiazepine agents have distinct pharmacological profiles, which are related to their different binding affinities for various $GABA_AR$ isoform configurations[65]. The endogenous equivalents to benzodiazepines are endozepines[66,67], which are released by astrocytes and are able to positively modulate GABAergic signalling[68,69].

Effective binding of benzodiazepines to $GABA_AR$ depends upon a key histidine residue within the α-subunit[70]. This residue is present in all isoforms of the α-subunit except α_4 and α_6 (REF.[71]), and newer benzodiazepine agents are able to target specific isoforms[52]. Upon binding, benzodiazepine increases the affinity of the receptor to GABA[72–74], which results in an increase in the frequency of channel opening, thereby increasing the conductance of the $GABA_AR$[75]. Under typical conditions, this increase facilitates the influx of negatively charged Cl^- ions, making it less

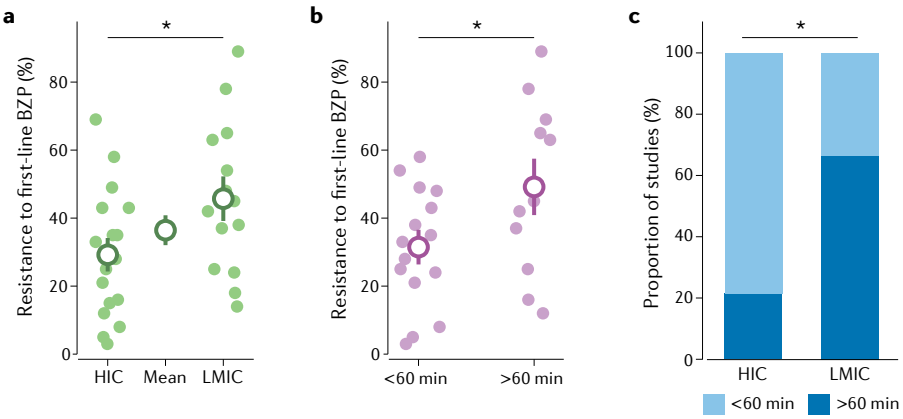

Fig. 1 | **Socioeconomic and temporal differences in benzodiazepine-resistant convulsive status epilepticus. a** | Reported resistance to first-line benzodiazepines (BZPs) in studies of convulsive status epilepticus (CSE) across countries with different economic profiles. The average rate of resistance to first-line BZPs was higher in studies from low-income and middle-income countries (LMIC) than in studies from high-income countries (HIC), as defined by the most recent World Bank Country and Lending Groups[216] (mean ± s.e.m. 45.71 ± 5.97% in LMIC versus 28.39 ± 4.26% in HIC; $P = 0.02$, unpaired *t*-test). The mean ± s.e.m. reported resistance to BZPs across all studies was 35.97 ± 3.81%. **b** | The average rate of resistance to first-line BZPs was higher in studies in which the mean duration of CSE before first-line treatment was more than 60 min than in studies in which the mean duration of CSE was less than 60 min (mean ± s.e.m. 49.18 ± 7.71 min for >60 min duration versus 31.47 ± 4.51 min for <60 min duration; $P = 0.03$, unpaired *t*-test). **c** | Compared with those from HIC, studies from LMIC were more likely to report a mean duration of CSE prior to first-line treatment that was >60 min (66.67% versus 21.43%; OR 7.33, $P = 0.04$, Fisher's exact test). The original data and analysis code used to generate these plots are available at https://github.com/richardjburman/bzp_review. See Supplementary Fig. 1 for stratification of studies according to the age group and number of study participants (weighted point estimates and error margins are included). *$P < 0.05$.

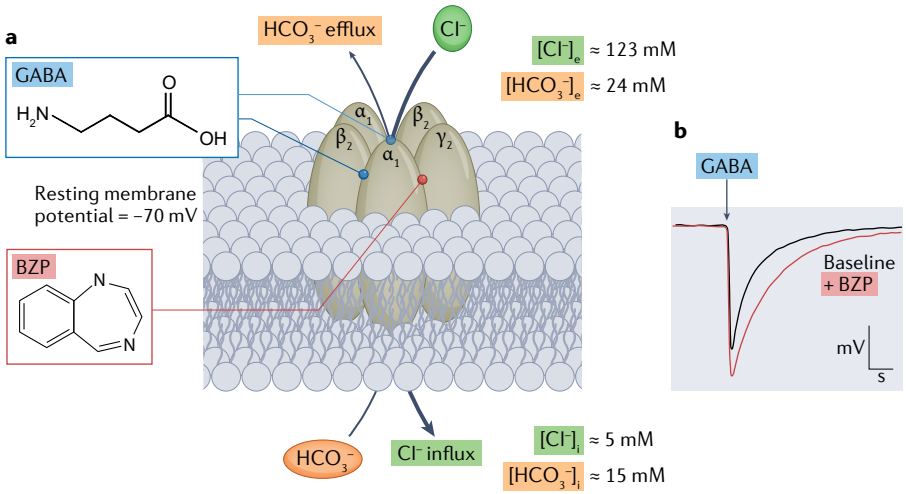

Fig. 2 | **Benzodiazepines bind to Cl^--permeable $GABA_A$Rs and enhance channel conductance.** **a** | The $GABA_A$ receptor ($GABA_A$R) is a pentameric channel that is found on the neuronal membrane and is formed of different combinations of subunits, with the most common configuration being α_1, β_2, γ_2, α_1 and β_2. The channel is activated by the binding of the neurotransmitter γ-amino butyric acid (GABA) at the junction between α_1- and β_2-subunits. Therefore, in the most common configuration of $GABA_A$R (illustrated), there are two GABA binding sites. The open channel allows Cl^- (green) and HCO_3^- (orange) flux along their respective electrochemical gradients and is four times more permeable to Cl^- ions than to HCO_3^- ions. Under typical conditions (that is, when the resting membrane potential is approximately −70 mV), $GABA_A$Rs permit Cl^- influx (thick arrow) and HCO_3^- efflux (thin arrow). The benzodiazepines (BZP) are a class of $GABA_A$R allosteric modulators that bind the $GABA_A$R at the junction of its α_1- and γ_2-subunits. Under baseline conditions the intracellular concentration of Cl^- ($[Cl^-]_i$) is typically low. **b** | When $GABA_A$Rs are activated, the predominant flux of ions is Cl^- movement down its electrochemical gradient into the cell. This influx of negative charge causes a membrane hyperpolarization referred to as an inhibitory postsynaptic potential (IPSP, black trace). BZPs broadly increase the conductance of the $GABA_A$Rs by increasing the frequency at which the $GABA_A$R opens, thus increasing the amplitude and duration of the IPSP (red trace). $[Cl^-]_e$, extraneuronal concentration of chloride; $[HCO^-]_e$, extraneuronal concentration of bicarbonate; $[HCO^-]_i$, intraneuronal concentration of bicarbonate.

likely that neurons fire action potentials (FIG. 2b). This is the putative mechanism by which benzodiazepines are thought to stop seizures. The ultimate effect of benzodiazepines, however, is dependent on the functional properties of $GABA_A$Rs, which can change with progressive seizure activity as discussed below.

What causes benzodiazepine resistance?

The pathophysiology of benzodiazepine resistance during status epilepticus can be broadly classified as having either inherited or acquired causes. The inherited causes relate to mutations in the genes that encode $GABA_A$Rs (BOX 1). The acquired causes can be further subclassified. The first subclass relates to the pharmacokinetic and pharmacodynamic tolerance to benzodiazepines that occurs independent of status epilepticus (BOX 2). The second subclass of acquired causes relates to the changes in $GABA_A$R physiology driven by the network hyperexcitability that occurs during status epilepticus. Although these different aspects are likely to operate in concert, this Review focuses specifically on the activity-dependent changes to the $GABA_A$R that occur throughout the evolution of status epilepticus.

The transmembrane Cl^- gradient

The $GABA_A$R is primarily a Cl^- channel. Therefore, the effects of modulating its conductance via benzodiazepine binding are governed by the state of the transmembrane Cl^- concentration gradient. Overwhelming evidence from in vivo studies in animals and in vitro studies using both animal and human tissue shows that this gradient is dynamic and can change considerably as a function of development and the state of network activity[76–82]. These changes have implications for benzodiazepine resistance, as discussed below.

The resting gradient. The resting transmembrane Cl^- gradient, and consequently the Cl^- equilibrium potential, is established by multiple cellular factors including the Na^+/K^+ ATPase, impermeant anions, Cl^- conductances and Cl^-–cation co-transporters[76–78,83–85]. However, only active or secondary active transport mechanisms for Cl^-, such as the Cl^-–cation co-transporters, are able to establish a driving force for Cl^-[78,83,86–88]. That is, they are able to shift the Cl^- equilibrium potential away from the resting membrane potential, thereby controlling the properties of $GABA_A$R-mediated signalling. The Na^+–K^+–Cl^- co-transporter (NKCC1) typically results in Cl^- influx and a more positive Cl^- equilibrium potential relative to the resting membrane potential, whereas the K^+–Cl^- co-transporter 2 (KCC2) extrudes Cl^-, resulting in a more negative Cl^- equilibrium potential relative to the resting membrane potential. These Cl^-–cation co-transporters are differentially expressed across development — in immature neurons, the levels of KCC2 expression are lower than the levels of NKCC1 expression[77]. This situation results in a higher intracellular concentration of Cl^- ($[Cl^-]_i$) in younger neurons, which causes GABAergic signalling to be depolarizing. As neural tissues mature, neurons upregulate KCC2 expression relative to NKCC1 expression[89]. In this mature state, Cl^- extrusion is increased, which results in a lower $[Cl^-]_i$ and an inhibitory shift in GABA function. In rodents, this transition from $GABA_A$R-mediated depolarization to hyperpolarization occurs during early postnatal life[90–93], whereas GABA has been reported to be already hyperpolarizing in healthy human cortex at term, presumably reflecting interspecies differences in rates of development[94–97]. Understanding the contributions of NKCC1 to development and disease is complicated by the fact that unlike KCC2, NKCC1 is also expressed in non-neuronal cells such as oligodendrocytes and endothelial cells, as shown by single-cell transcriptomic studies in rodents and humans[96,98,99]. This underscores the importance of functional evidence for the contribution of NKCC1 to $[Cl^-]_i$ and GABAergic responses in neuronal populations. For example, data from rodent brain slices indicate that NKCC1 contributes to subcellular effects, such as raised Cl^- levels in the axons of cortical pyramidal neurons[100], which support depolarizing GABAergic responses to inhibitory synaptic inputs that target the axon initial segment[101].

Effect of seizures. Seizures can change the expression and activity of both KCC2 and NKCC1, with these effects developing over tens of minutes to hours. Multiple in vitro studies using rodent brain tissue have shown that ongoing seizure activity induces a decrease in the function and surface expression of KCC2, which reduces the

Box 1 | Genetic mutations in $GABA_AR$s affect benzodiazepine sensitivity

Various mutations of the $GABA_A$ receptor ($GABA_AR$) directly affect benzodiazepine binding and could therefore contribute to benzodiazepine resistance in status epilepticus. A mutation in the γ_2-subunit, (γ_2(R43Q)), is known to increase the rate of desensitization of the receptor to benzodiazepines[217]. Mutations can also disrupt the interface between the γ- and β-subunits, negatively affecting channel function[72]. In addition, evidence indicates that some mutations can cause an increase in γ-subunit trafficking, thereby decreasing the availability or function of benzodiazepine-sensitive $GABA_AR$s at the synapse[218]. However, these mutations are typically associated with epileptic encephalopathies, such as Dravet syndrome[219,220], and are therefore likely to be relevant to benzodiazepine resistance in only a certain number of patients who develop status epilepticus in the context of distinct electroclinical syndromes.

Cl^- extrusion capacity of neurons[36,102–105]. This decrease is accompanied by an increase in the relative expression and activity of NKCC1 (REFS[106,107]). For example, in a study using rat hippocampal slices, the NKCC1 antagonist, bumetanide, was used to demonstrate the contribution of NKCC1 to depolarizing GABA responses in neurons following status epilepticus, and a corresponding shift in the ratio of KCC2 to NKCC1 mRNA expression was also observed[108]. Both of these changes were observed in ex vivo human brain tissue from patients with intractable epilepsy caused by different aetiologies when compared with control tissue that came from patients undergoing surgery for non-epilepsy-related brain pathology[109–112]. Therefore, prolonged seizure activity, of at least tens of minutes, seems to induce a reversal in the relative expression levels of Cl^-–cation co-transporters, resulting in expression patterns similar to those observed earlier in development. These changes increase baseline Cl^- levels, but also render neurons more susceptible to activity-induced Cl^- accumulation. Taken together, such alterations are predicted to weaken $GABA_AR$-mediated inhibition and thus reduce the potential for enhancing inhibition through allosteric modulation of the receptor by benzodiazepines.

Although Cl^-–cation co-transporters primarily determine the baseline $[Cl^-]_i$, they also influence whether Cl^- accumulates in neurons over shorter time scales (seconds to minutes), which is associated with increased network activity. During relatively quiescent periods, $[Cl^-]_i$ is low (typically around 5 mM), which equates to a reversal potential for the $GABA_AR$ (termed E_{GABA}) of approximately −70 mV. When $GABA_AR$s are activated, the transmembrane Cl^- gradient typically favours Cl^- influx, causing membrane hyperpolarization and an inhibitory action via the $GABA_AR$. KCC2 uses the transmembrane K^+ gradient to extrude Cl^- in order to maintain low $[Cl^-]_i$ and hence maintain E_{GABA} at levels negative to the resting membrane potential. Under these conditions, the inhibitory function of the $GABA_AR$ is preserved[60,104] (FIG. 3a).

Investigations in animal models have shown that an increase in network activity, whether physiological or during the build-up to seizures, causes enhanced synaptic GABA release and $GABA_AR$ activation[113,114]. This strong $GABA_AR$ activity generates large Cl^- influxes that cause rises in $[Cl^-]_i$[61,115–118]. Such Cl^- influx is enhanced when $GABA_AR$ activation is combined with concomitant membrane depolarization via glutamate receptors[119]. E_{GABA} therefore can become more positive relative to the resting membrane potential, although E_{GABA} might remain below the action potential threshold. In this state, $GABA_AR$-mediated inhibition is effectively weakened and will inhibit by "shunting" or facilitating the effects of simultaneous glutamate receptor activation, depending on the relative location and timing of synaptic inputs[120,121]. These conditions are accompanied by increased K^+ extrusion and a rise in the concentration of extraneuronal potassium ($[K^+]_e$)[122] (FIG. 3b). If network activity increases further, as is seen during seizures, the combined effect of increasing $[Cl^-]_i$ and $[K^+]_e$ can overwhelm the Cl^- extrusion capabilities of KCC2 (REF.[123]). This increased Cl^- accumulation depolarizes E_{GABA} beyond the action potential threshold[36,124]. In this state, subsequent $GABA_AR$ activation can be sufficiently depolarizing that it will trigger action potentials[36,124]. In other words, GABAergic signalling will have become excitatory (FIG. 3c).

Therefore, activity-dependent (that is, seizure-dependent) changes in $[Cl^-]_i$ can subvert $GABA_AR$ inhibitory signalling and sustain abnormal network activity. This short-term change in $GABA_AR$ signalling as a function of a change in the transmembrane Cl^- gradient has been referred to as 'short-term ionic plasticity'[77,81,119]. Such short-term, activity-dependent excitatory shifts in GABAergic signalling can occur during both self-terminating and self-perpetuating seizures[36,123–127]. This process is further aggravated by seizure-induced changes in the expression of Cl^-–cation co-transporters

Box 2 | Benzodiazepine-related pharmacokinetic and pharmacodynamic tolerance

Acute or previous chronic exposure to benzodiazepines or other compounds (including anti-seizure medications) can reduce the efficacy of benzodiazepines, with individualized susceptibility to this phenomenon[221,222]. Evidence from both experimental and clinical studies demonstrates that this reduction in efficacy can initially occur by induction of pharmacokinetic tolerance[223]. In this context, pharmacokinetic tolerance refers to any mechanism by which other medications change the bioavailability of the benzodiazepines. For example, many anti-seizure medications share common breakdown pathways via the cytochrome P450 enzyme system[224,225]. People with epilepsy who have previously received treatment with, for example, carbamazepine, phenytoin and phenobarbital (all known to induce the cytochrome P450) are likely to need higher doses of benzodiazepines as first-line agents to treat status epilepticus, owing to the induced increase in the ability to break down benzodiazepines[226]. Another important consideration is the baseline physiology of the patient and any other comorbid diseases (especially those affecting hepatic and renal function) that would further impact the metabolism of benzodiazepines[227].

By contrast, pharmacodynamic tolerance refers to how the sensitivity of the $GABA_AR$ to benzodiazepine changes after acute or chronic exposure[228]. Evidence from animals and humans shows that both short-term and long-term benzodiazepine use causes changes within the CNS that ultimately affect the ability of the $GABA_AR$s to be positively modulated by these agents[221,228–230]. Multiple studies have demonstrated how tolerance to the sedative, hypnotic and anti-seizure effects of benzodiazepines can emerge relatively rapidly, while the anxiolytic effects appear to be more resistant[231–233]. Evidence from animal and human studies suggests that continued benzodiazepine use could drive multiple downstream effects that culminate in benzodiazepine tolerance. First, persistent exposure to benzodiazepines leads to a loss of allosteric coupling between GABA and benzodiazepine binding sites on the $GABA_AR$, potentially via changes in receptor assembly or phosphorylation patterns[234]. Second, there might be alterations in the assembly, membrane trafficking and synaptic accumulation of $GABA_AR$s[235]. Third, there might be compensatory changes in glutamatergic neurotransmission[236]. Fourth, there might be interactions between various G-protein-coupled receptors and the $GABA_AR$ through concurrent activation of serotonergic[237], dopaminergic[238] and muscarinic[239] pathways. Last, benzodiazepines have also been shown to cause changes in neurosteroid signalling[240].

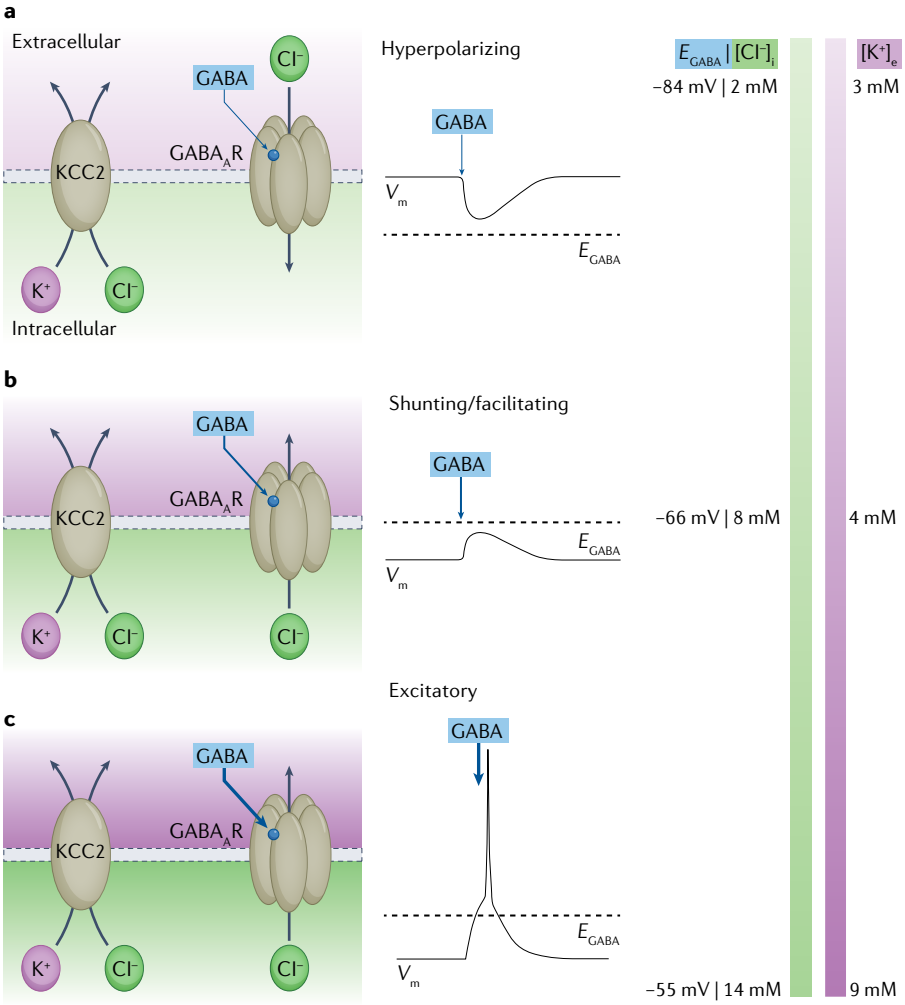

Fig. 3 | **Changes in intracellular Cl^- concentration set the properties of $GABA_A$R-mediated signalling. a** | At rest, the concentration of intraneuronal chloride ($[Cl^-]_i$; green) is low and the reversal potential for GABA (E_{GABA}) is hyperpolarized relative to the resting membrane potential (V_m). This situation allows Cl^- influx and membrane hyperpolarization upon GABA binding to the $GABA_A$ receptor ($GABA_A$R). The low concentration of extraneuronal potassium ($[K^+]_e$; purple) allows efficient potassium–chloride co-transporter 2 (KCC2)-mediated extrusion of Cl^-. **b** | During states of increased network activity, more GABA is released into the synaptic cleft leading to enhanced $GABA_A$R activation, greater Cl^- influx and a rise in $[Cl^-]_i$, shifting the E_{GABA} to sit above V_m, but below the action potential threshold. Subsequent $GABA_A$R activation can then result in net anion efflux and GABA-mediated shunting or facilitation of accompanying glutamatergic synaptic input (shunting or facilitation occurs when $GABA_A$R-mediated conductances reduce or enhance the depolarization caused by concurrent glutamate receptor activation). Increased KCC2 activity occurs to correct for the raised $[Cl^-]_i$, which can lead to increased $[K^+]_e$. $[K^+]_e$ is also increased by K^+ efflux via other channels during network activity. **c** | When hyperexcitability is sustained, Cl^- accumulation can be so severe that E_{GABA} shifts above the action potential threshold and $GABA_A$R activation becomes excitatory and can trigger action potentials. The rising $[K^+]_e$ reduces the transmembrane K^+ gradient further, which impedes KCC2 function and facilitates the rise in $[Cl^-]_i$.

(mentioned above), which make neurons more susceptible to Cl^- accumulation. BOX 3 discusses the role of Cl^- in seizure pathogenesis and efforts to target this process therapeutically.

Alterations to $GABA_A$R

During status epilepticus there seems to be internalization and reconfiguration of the $GABA_A$R that leads to a marked reduction in benzodiazepine sensitivity starting several minutes after the onset of seizure activity. In several studies using in vivo animal models, increased mobility and internalization of the synaptic, benzodiazepine-sensitive configuration of the $GABA_A$R was observed after 10 min of status epilepticus[128–131]. This phenomenon was observed with different techniques in cell culture and acute brain slice preparations using both optical and electrophysiological measures of $GABA_A$R function. More specifically, seizure activity caused a downregulation of the α_{1-4}-, β_{2-3}- and γ_2-subunits, which are essential for the formation of the benzodiazepine binding site[129,131,132]. Concurrently, the expression of extrasynaptic, benzodiazepine-insensitive $GABA_A$Rs increased, as demonstrated by an observed upregulation of the α_5- and δ-subunits that are important components of extrasynaptic $GABA_A$Rs and responsible for tonic inhibition[130,131,133] (FIG. 4). Collectively, these processes represent an acquired change in $GABA_A$R structure that contributes to benzodiazepine resistance occurring over the course of minutes to hours of ongoing seizure activity.

Although the results of studies in animals indicate that receptor internalization can start to develop after 10 min of status epilepticus[134], this internalization becomes progressively more pronounced after 30 min[130] and 60 min[128]. These seizure-induced changes in the benzodiazepine sensitivity of $GABA_A$R can be long-lasting. For example, in resected brain tissue from individuals who have multidrug-resistant temporal lobe epilepsy and have experienced recurrent seizures for many years, expression of $GABA_A$Rs with benzodiazepine binding sites was lower than in tissue from autopsies of individuals without neurological conditions[135,136]. In PET studies, which allow the analysis of human $GABA_A$R composition in vivo, participants with refractory epilepsy had a decrease in benzodiazepine-binding affinity at the site of seizure origin — the so-called ictogenic focus[137,138].

Effect on benzodiazepine efficacy

Under the conditions of profound Cl^- loading that occur during seizures and status epilepticus in animal models, benzodiazepines are predicted to lose their efficacy or even perhaps exacerbate seizure-like activity by enhancing excitatory GABAergic signalling[36,124,126,139]. In a study using dissociated rat neuronal cultures, Cl^- accumulation during ongoing network activity was associated with a reduced inhibitory effect of diazepam[139]. More recently, in a study using in vitro rodent brain slice models, status epilepticus-induced increases in Cl^- and the resulting excitatory shift in GABAergic signalling were associated with a progressive loss in the efficacy of diazepam[36]. In addition, in brain slices with progressive status epilepticus-like activity and Cl^--loaded neurons, the application of diazepam exacerbated the severity of epileptiform discharges. Last, in a study in rats, pharmacologically blocking NKCC1

Box 3 | **Role of Cl^- in the pathogenesis of status epilepticus**

Computational modelling of ion dynamics during seizures has implicated increasing levels of intraneuronal Cl^- in extending seizure activity and contributing to the development of status epilepticus[241]. The important role of Cl^- in the pathogenesis of status epilepticus and efforts to manipulate Cl^- extrusion are, therefore, of increasing therapeutic interest[242,243]. For example, recent studies have explored manipulating Cl^- influx and efflux to study how this affects the evolution of seizure activity. Attempts have been made to modulate KCC2 function through overexpression[244] or by preventing seizure-induced phosphorylation-dependent KCC2 inactivation[245], with both approaches significantly limiting the severity of seizure activity.

rescued benzodiazepine sensitivity in status epilepticus[140].

Taken together, these data suggest that during status epilepticus there is a preferential shift away from phasic, benzodiazepine-sensitive GABAergic inhibition, towards tonic, benzodiazepine-insensitive GABAergic excitation. Multiple processes are involved and are likely to occur in parallel across different timescales from minutes to hours (FIG. 5). In our opinion, these insights gleaned from basic epilepsy research are likely to explain the clinical phenomenon of progressive benzodiazepine resistance that emerges in status epilepticus of prolonged duration (FIG. 1b). Changes to the $GABA_AR$ configuration and the capability of neurons to extrude Cl^- are also likely to persist after the termination of status epilepticus, potentially contributing to the development of epilepsy and persistent benzodiazepine insensitivity in affected individuals.

Role of glutamatergic signalling

The changes in the function of $GABA_AR$-mediated inhibition during status epilepticus are also linked to glutamatergic signalling through the *N*-methyl-D-aspartate receptor (NMDAR). It has been shown in a rodent hippocampal culture model of status epilepticus that prolonged seizure activity causes a widespread and persistent activation of NMDARs that initiates an increase in intracellular calcium concentration ($[Ca^{2+}]_i$)[141]. This rise in $[Ca^{2+}]_i$ has then been shown to activate multiple second-messenger pathways (for example, protein kinase C, calcineurin and extracellular signal-regulated kinases), which can decrease the expression of both phasic and tonic $GABA_ARs$ through complementary pathways[131,142–145]. In addition, evidence from rat neuronal cultures indicates that NMDAR-mediated Ca^{2+} influx can downregulate KCC2 function, thereby reducing the inhibitory capacity of the $GABA_ARs$ that are expressed[103]. Furthermore, the elevated $[Ca^{2+}]_i$ has been implicated in the activation of mechanisms that upregulate the expression of NMDARs as well as the other main glutamatergic receptor, the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)[129,146]. The net result is an enhancement of glutamatergic excitation combined with a reduction in $GABA_AR$-mediated inhibition which serves to both exacerbate the ongoing seizure activity and severely compromise the efficacy of benzodiazepines[147].

Is a new treatment approach needed?

The experimental data discussed above suggest that resistance to benzodiazepines involves multiple mechanisms that affect $GABA_AR$ function and operate on a range of timescales, including the timescale of an individual status epilepticus episode. This view is supported by the clinical observation that episodes of status epilepticus longer than 60 min seem to show greater resistance to benzodiazepines[14,36,37] (FIG. 1). Therefore, an argument could be made that patients who present in status epilepticus that has lasted over 60 min, or patients who have previously presented in status epilepticus, might benefit from a more tailored treatment approach that does not include benzodiazepines as first-line management. Such a strategy might speed up the delivery of the most efficacious interventions and thus help reduce the morbidity and mortality associated with prolonged status epilepticus. Although this concept is appealing in theory, currently no clinical evidence exists to support the use of alternative anti-seizure medications as first-line management of status epilepticus. Therefore, benzodiazepines remain the gold standard as they are cheap, safe and effective, if given at the correct time and at an adequate dose.

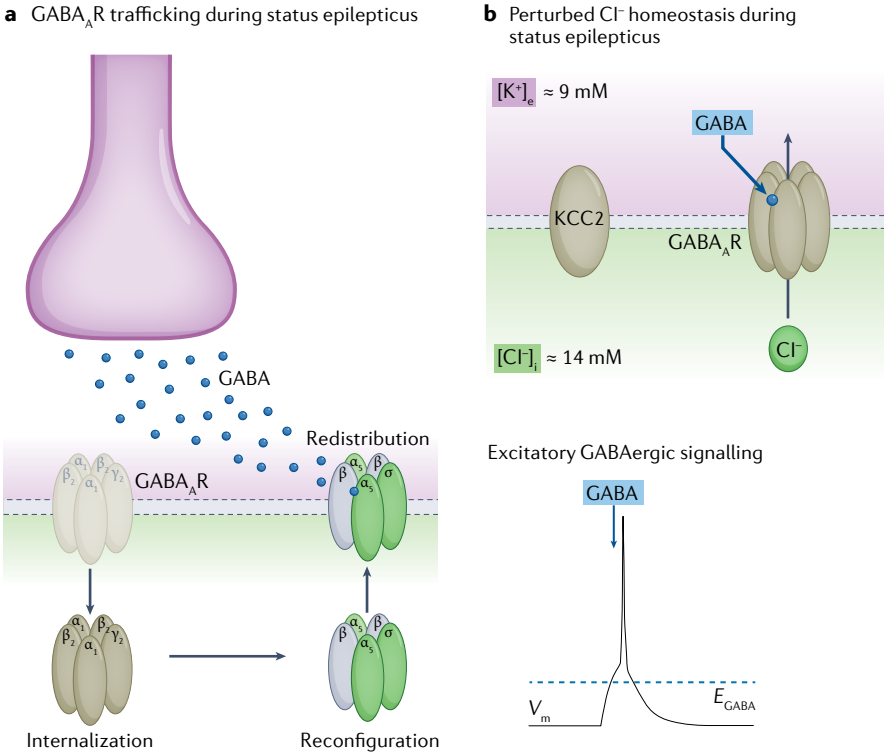

Fig. 4 | **Status epilepticus causes disruptions to $GABA_AR$ composition and function. a** | During status epilepticus, the $GABA_A$ receptor ($GABA_AR$) undergoes endocytosis-mediated internalization. Once internalized, $GABA_ARs$ are reconfigured with subunits that are insensitive to benzodiazepines (green) and are preferentially redistributed to extrasynaptic locations. **b** | Status epilepticus leads to an activity-dependent increase in the concentration of intraneuronal chloride ($[Cl^-]_i$) and extraneuronal potassium ($[K^+]_e$), as well as an acquired dysfunction of the potassium–chloride co-transporter (KCC2). Together, these events lead to a depolarizing shift in the Cl^- electrochemical gradient that can cause $GABA_AR$ activation to become excitatory.

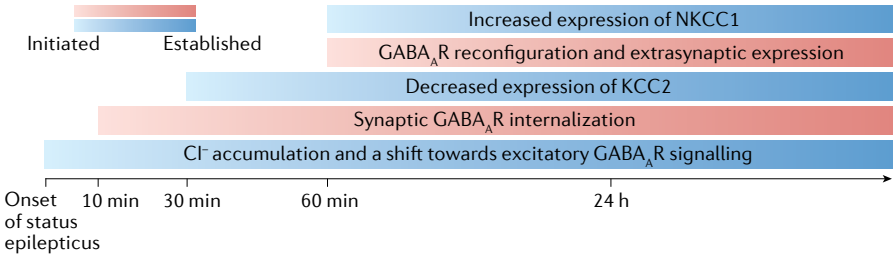

Fig. 5 | **Proposed timeline of changes affecting benzodiazepine efficacy during status epilepticus.** Changes to Cl^- homeostasis are shown in blue and changes to $GABA_A$ receptor ($GABA_AR$) expression are shown in red. KCC2, potassium–chloride co-transporter; NKCC1, sodium–potassium–chloride co-transporter.

However, if we were to consider a possible candidate as an alternative first-line treatment, what should this be? One rational approach to this question would be to consider the most effective second-line agent in the case of benzodiazepine resistance in status epilepticus. In the past 3 years, large multicentre studies have explored the efficacy of second-line agents in both adult and paediatric patients with CSE[9–11]. In the Established Status Epilepticus Treatment Trial (ESETT), the results of which were published in 2019, more than 50% of participants who received second-line treatment with levetiracetam, valproate or fosphenytoin did not respond to treatment[9,31]. One agent, however, that has been excluded from the recent multicentre studies as a second-line treatment option is phenobarbital. Evidence from an in vitro model of status epilepticus-like activity in rodent brain slices has shown that at low doses phenobarbital augments epileptiform activity[36]. This effect is likely to result from low-dose phenobarbital having a strong $GABA_AR$ agonist[43] effect, which renders it vulnerable to the same changes in $GABA_AR$ physiology that affect the action of benzodiazepines. However, at high doses, phenobarbital seems to be very effective at terminating persistent status epilepticus-like activity in animal models[36]. This action is attributed to pharmacological effects other than its action on $GABA_ARs$ — at higher concentrations, phenobarbital is also an effective antagonist of AMPA and kainate glutamatergic receptors[148–150]. Therefore, phenobarbital might maintain anti-seizure activity, even in brain areas of modified $GABA_AR$ expression or with profound intraneuronal Cl^- accumulation.

Phenobarbital has been shown to be an effective agent for the treatment of refractory CSE and is still widely used in resource-limited health-care systems[8,151]. For example, in a cohort of adult patients presenting with benzodiazepine-resistant CSE in China, intravenous phenobarbital was effective in 81% of the participants who received it, whereas intravenous valproate was only effective in 44% of treated participants[151]. In a study of paediatric patients with benzodiazepine-resistant CSE in a resource-limited setting, phenobarbital was effective in 86% of patients and was more effective than the more widely used phenytoin[8]. A concern exists that respiratory depression can follow a bolus injection of phenobarbital. However, evidence indicates that this adverse event occurs in a small number of patients — ~13% of treated adults[152] and ~14% of treated children[8] — which does not seem to be significantly different from its occurrence following treatment with other anti-seizure medications such as levetiracetam (~8% of treated adults[9] and ~10% of treated children[10]), fosphenytoin (~13% of treated adults[9]), phenytoin (~11% of treated children[10]) and valproate (~8% of treated adults[9]).

Chronic treatment with phenobarbital can be associated with neurobehavioural and cognitive adverse effects[153–159]. However, the evidence does not suggest that the same occurs when phenobarbital is used in an acute setting[160–164]. This information should inform cost–benefit calculations to decide whether the need to stop status epilepticus outweighs the potential negative effects of phenobarbital on cognition. These kinds of calculations are already well established in other clinical situations, such as the acute use of valproate to manage status epilepticus in pregnant women despite its well-known teratogenicity[165]. A major barrier to the further use of phenobarbital, especially in resource-limited countries, is that suppliers have reduced production owing to the limited profitability and the restrictive regulations for access to barbiturates[166].

Last, one might also consider moving away from first-line monotherapy with benzodiazepines and instead combine them with other agents that exhibit synergistic effects. There are new, emerging treatment options that target more specific mechanisms of status epilepticus pathophysiology than current treatment protocols and might prove to be effective for the safe termination of status epilepticus[167–169]. Specifically, clinically available agents that target NMDARs (that is, ketamine) and AMPARs (that is, perampanel) are appealing prospects as these receptors seem to be upregulated in status epilepticus, and also contribute to the degradation of $GABA_AR$-mediated inhibition[170–172]. To date, the evidence is insufficient to support the use of these agents in the early management of status epilepticus, but this situation might change with the completion of ongoing clinical trials[173–175]. Encouraging evidence from animal studies indicates a revival of benzodiazepine efficacy in models of resistant status epilepticus when benzodiazepines are combined with agents that target other systems. These include the combination of a benzodiazepine (either diazepam or lorazepam) with the NMDAR competitive antagonist 3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid[176] or the K^+ channel activator flupirtine[177]. Further clinical studies into the use of these synergistic treatment combinations are needed and for now benzodiazepines remain the gold standard for first-line management of status epilepticus.

Unanswered questions

In this Perspective article, we have presented both clinical and experimental data that highlight the importance of

Box 4 | **Non-convulsive status epilepticus**

Non-convulsive status epilepticus (NCSE) occurs when there is continuous or repetitive seizure activity seen electrographically with or without cognitive and behavioural changes, but without any motor (convulsive) manifestations[4,246]. Convulsive status epilepticus (CSE) and NCSE can exist in a continuum, whereby a patient can transition from CSE to NCSE, and vice versa. Unlike the vast amount of literature on the use of benzodiazepine in the management of CSE, there is a dearth of studies on the management of NCSE. This situation is likely to be a result of the difficulties in diagnosing this NCSE outside a setting where there is access to continuous EEG monitoring[247]. Overall, 67% of patients in NCSE do not respond to first-line treatment with benzodiazepines[152,248–250]. This rate is approximately 1.5 times higher than that of CSE and is likely, at least in part, to result from delays in recognition and treatment initiation for NCSE.

Box 5 | **Neonatal status epilepticus**

Neonatal status epilepticus is best considered as a separate entity from paediatric and adult status epilepticus, as synaptic signalling mechanisms in neonates differ considerably from those in the paediatric and adult brain[78,217,251,252]. Expression of Cl^- co-transporters changes during development[76], which could result in higher levels of Cl^- in the neonatal brain than in the adult and paediatric brain. These high levels of Cl^- might cause GABAergic signalling to be less inhibitory and even depolarizing. This situation is combined with a relatively smaller contribution of glutamatergic synaptic activity under physiological conditions[253–256]. As development progresses, K^+–Cl^- co-transporter 2 (KCC2) is upregulated relative to Na^+–K^+–Cl^- co-transporter (NKCC1), lowering Cl^- and promoting inhibitory GABAergic signalling, which balances the associated maturation in the number and strength of glutamatergic synapses[257–260].

The result of higher intraneuronal Cl^- in the neonatal brain is that positive allosteric modulators of $GABA_A$ receptors ($GABA_AR$s) are less effective in terminating seizure activity, and could exacerbate status epilepticus[261]. For example, a common feature of neonatal status epilepticus is the absence of a clinical presentation to accompany the electrographic seizure activity, particularly in very sick or preterm neonates[262]. This phenomenon, often referred to as 'electroclinical uncoupling', can also be induced by the administration of $GABA_AR$ modulators such as benzodiazepines or low-dose phenobarbital[263–269]. Electroclinical uncoupling in neonates might be attributed to regional differences in intraneuronal Cl^- concentrations. For example, Glykys et al.[270] showed that a lower intraneuronal Cl^- favouring $GABA_AR$-mediated hyperpolarization emerges in subcortical regions before cortical regions in rodent in vitro models. This more nuanced understanding of GABAergic signalling in the neonatal brain, particularly regarding the potential role of neuronal NKCC1, has inspired further exploration into how manipulating this co-transporter might affect neonatal seizures and potentially rescue anti-seizure effects of $GABA_AR$ modulators[261,271–275,279]. Clinical trials have investigated whether blocking NKCC1 with bumetanide has a measurable clinical benefit on neonatal seizures[276,277]. However, owing to mixed outcomes and safety concerns, whether the use of adjuvant bumetanide is safe and effective in the management of neonatal status epilepticus is not yet known[278].

benzodiazepine-resistant CSE and provide information about some of the mechanisms that are likely to underlie this clinical phenomenon in adults and children. The relevance of these insights into other forms of status epilepticus, namely NCSE and neonatal status epilepticus are briefly discussed in BOX 4 and BOX 5.

Trying to bridge the gap between clinical and experimental domains of status epilepticus is a challenge and unanswered questions around how benzodiazepine responsiveness can vary across different types and durations of status epilepticus remain. For example, although experimental and clinical data provide an explanation of how benzodiazepine resistance increases with duration of status epilepticus, many individuals present in prolonged CSE and yet still respond to first-line benzodiazepines. Similarly, studies in both adults[13,178,179] and children[8,180] have shown that in many individuals who seem to be resistant to first-line treatment with benzodiazepines, such as intravenous lorazepam, rectal diazepam or intranasal midazolam, an infusion of midazolam or diazepam is able to successfully terminate the CSE[13]. This observation remains poorly understood. On the basis of information from experimental studies, one possible explanation for the inter-individual variation in benzodiazepine sensitivity is that across the brain there are differential responses to these agents, with some areas being benzodiazepine-resistant and other areas remaining benzodiazepine-sensitive (FIG. 6). For example, in actively seizing neuronal networks with raised $[Cl^-]_i$ and $[K^+]_e$, GABAergic signalling would be excitatory and benzodiazepines ineffective. In contrast, in other less-affected areas, $[Cl^-]_i$ might be low and GABAergic inhibition would be intact; thus a benzodiazepine would enhance inhibition in these brain areas. The combined effect of a benzodiazepine would therefore be a function of which, and to what extent, different brain areas have been recruited into the seizure. These ideas are supported by computational modelling studies of seizure propagation dynamics that demonstrate how area-specific inhibitory capacity directs the temporal and spatial spread of activity[181,182].

Translation from 'bench to bedside' is rarely seamless. This challenge is evident in the numerous potential novel treatments that work in animal models of status epilepticus but fail to generate any meaningful clinical benefit when tested in patients. One example of this kind of situation is the use of bumetanide to treat neonatal status epilepticus (BOX 5). Similarly, the neurosteroid allopregnanolone, which selectively targets extrasynaptic $GABA_AR$[183], had anti-seizure effects in both acute and chronic animal models of seizures[184]. However, studies of this agent for the management of status epilepticus in humans have produced conflicting results[185–187] and neurosteroids are not conventionally used in the current management of status epilepticus. Learning from the examples of bumetanide and allopregnanolone, therefore, excitement should be tempered when preclinical studies reveal new potential treatments. Instead, we should continue to exercise patience until high-quality clinical data are available.

Concluding remarks

Benzodiazepine resistance remains a pressing, global clinical problem within the management of status epilepticus. Clinical studies have shown that the duration of status epilepticus before first treatment is an important factor in determining the likelihood of benzodiazepine resistance. This conclusion is supported by evidence from animal models, which demonstrates

Glossary

Co-transporters
Transmembrane proteins that allow the coupled, simultaneous transport of multiple substances across the membrane.

Equilibrium potential
The electrical potential difference at which the flow of ions down their transmembrane concentration gradient is exactly balanced by the opposing potential difference across the membrane; at the equilibrium potential there is no net flux of ions.

Ionotropic receptor
A ligand-gated ion channel in which ligand binding results in transmembrane ion flux through the receptor's pore.

Phasic inhibition
The fast activation of synaptic $GABA_A$ receptors following pre-synaptic release of GABA.

Resting membrane potential
The electrical potential difference across the cell membrane at rest (that is, when the cell is not receiving synaptic input or engaged in action potential firing).

Secondary active transport
The transport of chemical substances across a membrane (also known as co-transport), where the energy to move one substance against its concentration gradient is provided by the movement of another substance down its concentration gradient.

Shunting
A type of inhibition whereby activated $GABA_A$ receptors lower the local membrane resistance, which reduces (or 'shunts') the impact of concurrent excitatory synaptic inputs.

Tonic inhibition
The continuous activation of perisynaptic and extrasynaptic $GABA_A$ receptors owing to the presence of ambient GABA in the extracellular space, or spontaneous $GABA_A$ receptor openings.

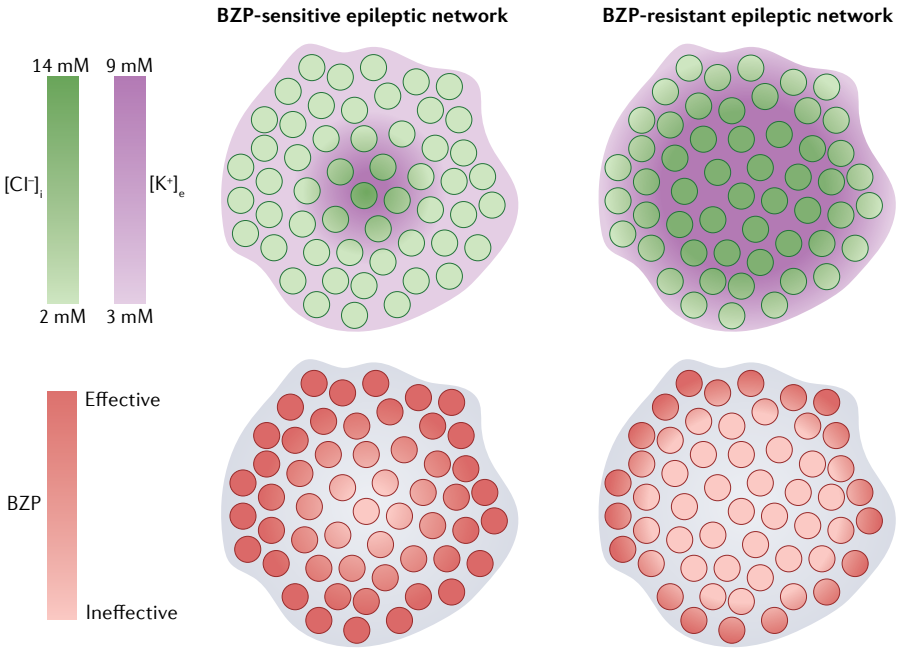

Fig. 6 | **Spatial dynamics of activity-dependent shifts in $[Cl^-]_i$ and $[K^+]_e$ might explain different responses to benzodiazepines.** The images show different epileptic networks, one that is sensitive to benzodiazepines (BZPs, left) and one that is resistant to BZPs (right). Neurons in the network are represented by circles. If the seizure focus is surrounded by areas with intact chloride (Cl^-) and potassium (K^+) transmembrane gradients (left), BZPs might be effective in preventing seizure propagation and thereby facilitate termination. If, however, these gradients are compromised in a large enough area (right), BZPs would be ineffective in stopping seizure activity and could even help maintain seizure activity via excitatory GABAergic signalling. $[Cl^-]_i$, intraneuronal chloride; $[K^+]_e$, extraneuronal potassium.

that during persistent seizure activity, GABAergic synaptic transmission alters in multiple ways that can contribute to progressive benzodiazepine resistance. Although some inconsistencies remain between clinical and experimental studies, evidence suggests that the time since onset of status epilepticus should be considered as a critical factor in determining the probability of benzodiazepine responsiveness, and in status epilepticus that is prolonged at presentation, adjunctive therapy should be considered very early. An understanding of the cellular and molecular mechanisms underlying benzodiazepine resistance gleaned from experimental studies should inform the optimization of future strategies for managing status epilepticus.

Code availability

All code used to generate FIG. 1 and Supplementary Fig. 1 can be accessed at https://github.com/richardjburman/bzp_review.

Data availability

All data used to generate FIG. 1 and Supplementary Fig. 1. can be accessed at https://github.com/richardjburman/bzp_review.

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R.J.B and J.V.R. researched data for the article, made a substantial contribution to discussion of content, wrote the article, and reviewed and edited the manuscript before submission. All other authors made a substantial contribution to discussion of content, wrote the article, and reviewed and edited the manuscript before submission.

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The authors declare no competing interests.

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Review criteria
The studies mentioned in Table 1 were found using medical search headings (MeSH) on the PubMed and Embase database search platforms. We searched within the main heading of 'convulsive status epilepticus' and included 'drug therapy' and 'prevention and control' as subheadings. We added 'benzodiazepines' with the subheadings 'administration and dosage' and 'therapeutic use' to our search requirements. We limited our search to studies published from 1 January 1990 to 1 July 2021 and to peer-reviewed studies that were published in English and had the full text available. Studies were included if they were performed in patients, both adult and/or paediatric, presenting in convulsive status epilepticus and where monotherapy with a benzodiazepine (consisting of one or two doses), of any kind or formulation, was assessed in terms of its efficacy in terminating status epilepticus. In addition to this search, we also assessed the studies mentioned in two systematic reviews[7,188] and added additional studies that met our inclusion criteria.

Supplementary information
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