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Recommendations for treatment strategies in people with epilepsy during times of shortage of antiseizure medications

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ABSTRACT

In times of severe antiseizure medication (ASM) shortage due to emergency situations (*e.g.*, disasters, conflicts, sudden disruption to international supply chains), management of people with epilepsy with available ASMs can be difficult. A group of experts was brought together by the International League Against Epilepsy (ILAE) to formulate recommendations for such circumstances. Every effort was made to base these recommendations on direct published literature or extrapolations from basic information available about ASMs. Actual published literature in this area is, however, limited, and at times, assumptions were made by the experts to generate these recommendations. During times of shortage of ASMs, switching between different ASMs (*e.g.*, oxcarbazepine and carbamazepine) can occasionally be considered as a mitigation procedure. However, for many ASMs, the option of an overnight switch to another drug does not exist. Switching from brand to generic or between generic products has often been shown to be safe, if required. Finally, when supplies of benzodiazepines or equipment to administer medications intravenously are not available, rectal administration of some ASMs may be an emergency alternative route for treating serial seizures and status epilepticus. Decision-making with regard to treatment and possible options should be driven by what is best for the patient.

Key words: antiseizure, antiepileptic, drug, epilepsy, seizure

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This narrative review provides recommendations for managing people with epilepsy (PWE) in times of severe antiseizure medication (ASM) shortages due to emergency situations (*e.g.*, conflicts, disease outbreaks, sudden disruption to international supply chains, *etc.*) or defective health systems (*e.g.* poor planning, lack of data to inform ordering, economic crises, *etc.*). A group of experts (brought together by the International League Against

Epilepsy [ILAE]) collaborated (through online meetings and e-mail communications) to put together these recommendations. Every effort was made to base the provided suggestions on direct published literature or extrapolations from the existing information about ASMs. In doing so, we searched the PubMed in April 2020 with the following key words: "seizure or epilepsy" and "treatment or drug or medication" and "shortage or resources or access". Actual published literature in this area is limited and at times, assumptions were required by the experts to generate these recommendations. The care and well-being of the patient and the treatment of her/his epilepsy should be of paramount concern for all healthcare professionals dealing with PWE. Changes from one ASM to another, even when within the same group of medications, may be associated with a seizure recurrence risk and with the risk of adverse effects [1]. These risks have to be taken into consideration and the patient should be informed about the best practice in such an emergency situation. As always, decision-making regarding treatment and possible options is driven in this setting by what is best for the patient.

Mitigation procedures during times of shortage of ASMs

During times of shortage of ASMs, switching between different ASMs can occasionally be considered as a mitigation procedure. The following material is a summary of such procedures, based on the available evidence and expert opinion.

Oxcarbazepine/carbamazepine

The usual daily maintenance dose of oxcarbazepine is approximately 1.5 times that of carbamazepine in adults and 1.2 times that of carbamazepine in the elderly [2, 3]. In case of need, the two medications can be directly switched instantly considering the above-mentioned ratios.

Eslicarbazepine acetate/oxcarbazepine/carbamazepine

The overnight transition between oxcarbazepine and eslicarbazepine acetate (or vice versa) in a 1:1 ratio is generally well tolerated [4-7]. The overnight transition between carbamazepine and eslicarbazepine acetate (or vice versa) in a ratio of 1:1.3-1.5 is reasonable [4]. In case of need, these drugs can be interchanged instantly considering the above-mentioned ratios.

Clobazam/clonazepam

Clonazepam is 10 to 20 times more potent than clobazam; therefore, 1 mg of clonazepam may be similar in potency to 10-20 mg of clobazam. In case of need, these two drugs can be interchanged instantly considering the above-mentioned ratio [8]. One should keep in mind that these two drugs may not have the same efficacy against various seizure types (*e.g.*, myoclonic seizures *vs.* focal seizures).

Brivaracetam/levetiracetam

Brivaracetam at 50 mg could be replaced by 1,000 mg levetiracetam, 100 mg of brivaracetam by 2,000 mg levetiracetam, and 200 mg of brivaracetam by 3,000 mg levetiracetam [9]. In case of need, these two drugs can be interchanged instantly considering the above-mentioned ratios.

Primidone/phenobarbital

Primidone is metabolized to phenobarbital and phenylethylmalonamide (PEMA). PEMA is also known to have anti-seizure properties. Studies estimate that about 24% of primidone is converted to phenobarbital. A switch of primidone to phenobarbital can be made (with a ratio of 4:1). However, in light of the additional anti-seizure properties of PEMA, consider giving an additional dose in the first 24 hours [10].

Other ASMs

For most other ASMs, the option of an overnight switch to another (similar) drug does not exist. However, in the circumstance of shortage of these ASMs, one can contemplate the following strategy. First, identify the epilepsy type and syndrome of the patient. Then, identify a list of the appropriate ASMs for that specific patient, considering their epilepsy (*e.g.*, generalized *vs.* focal or juvenile myoclonic epilepsy *vs.* juvenile absence epilepsy) (*table 1*) and other important variables (*e.g.*, age, sex, comedications, comorbidities, *etc.*). Next, in the setting of the shortage or unavailability of the currently taken ASM, start switching to another ASM (from the prepared list) with the following strategy. In any case, one should be familiar with the pharmacokinetic parameters of ASMs in order to design reasonable therapeutic plans for their patients (*tables 2, 3*) [2]. Some ASMs (as an alternative to the unavailable drug) can be initiated with the desired therapeutic doses (with no titration-up schedule). In such circumstances consider at least one overlapping dose (*table 4*) [2, 11, 12].

▼ **Table 1.** Some suggested antiseizure medications (ASMs) based on epilepsy syndromes/ seizure types.

Syndrome/ seizure type	Treatment options
Infantile epileptic spasms	ACTH, oral corticosteroids, vigabatrin, topiramate, lamotrigine, levetiracetam, nitrazepam, zonisamide
Lennox-Gastaut syndrome	Valproate, lamotrigine, topiramate, clobazam, levetiracetam, rufinamide, cannabidiol, zonisamide
Dravet syndrome	Valproate, stiripentol, clobazam, cannabidiol, topiramate, fenfluramine, phenobarbital, ethosuximide, levetiracetam Carbamazepine, phenytoin, vigabatrin, and lamotrigine should be avoided.
Epilepsy with myoclonic atonic seizures (Doose syndrome)	Valproate, lamotrigine, ethosuximide, benzodiazepines, acetazolamide, levetiracetam, rufinamide, topiramate Carbamazepine, phenytoin, and vigabatrin are contraindicated.
Progressive myoclonic epilepsies	Valproate, topiramate, benzodiazepines, phenobarbital, piracetam, levetiracetam For mitochondrial disorders, valproate is contraindicated.
Developmental and epileptic encephalopathy with spike-wave activation in sleep (formerly Landau-Kleffner syndrome)	Valproic acid, clobazam, ethosuximide, sulthiame, benzodiazepines, steroids. Carbamazepine and possibly phenobarbital and phenytoin may occasionally exacerbate the syndrome.
Self-limited epilepsy with centro-temporal spikes (SeLECTS; formerly known as benign rolandic epilepsy or benign epilepsy with centro-temporal spikes)	Carbamazepine, oxcarbazepine, gabapentin, valproate, lamotrigine, levetiracetam
Self-limited focal epilepsies (SeLFE) (*e.g.*, benign occipital epilepsies)	Valproate, levetiracetam, carbamazepine, clobazam
Childhood (CAE) and juvenile (JAE) absence epilepsies	Ethosuximide (in CAE), valproate (in JAE), lamotrigine, topiramate, zonisamide, acetazolamide, benzodiazepines
Juvenile myoclonic epilepsy (JME)	Valproate is the drug of first choice in men and levetiracetam is the drug of first choice in women of child-bearing potential. Lamotrigine, topiramate, zonisamide, benzodiazepines
Children with focal-onset seizures	Carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, lacosamide, zonisamide, brivaracetam, topiramate, perampanel
Adults with focal-onset seizures	Lamotrigine, levetiracetam, lacosamide, brivaracetam, carbamazepine, oxcarbazepine, eslicarbazepine acetate, phenytoin, topiramate, perampanel, phenobarbital, gabapentin, cenobamate, zonisamide
Elderly with focal-onset seizures	Lamotrigine, levetiracetam, lacosamide, gabapentin, zonisamide
Children with generalized tonic-clonic (GTC) seizures	Lamotrigine, brivaracetam, lacosamide, levetiracetam, topiramate, zonisamide, valproate, phenobarbital
Adults with GTC seizures	Valproate, lamotrigine, levetiracetam, lacosamide, brivaracetam, topiramate, zonisamide, oxcarbazepine, carbamazepine, perampanel, phenytoin, phenobarbital
Elderly with GTC seizures	Levetiracetam, lamotrigine, lacosamide
Atonic seizures	Valproate, topiramate, rufinamide, lamotrigine, levetiracetam, cannabidiol, phenobarbital, zonisamide
Tonic seizures	Valproate, topiramate, rufinamide, lamotrigine, clobazam, levetiracetam, cannabidiol, phenobarbital, zonisamide

Adapted from reference [2].

▼ **Table 2.** Pharmacokinetic parameters of commonly prescribed antiseizure medications (ASMs).

Drug	Absorption and Distribution	Metabolism and Excretion	Drug Interactions and Special Considerations
Carbamazepine (CBZ)	Bioavailability: 75% - 85% Volume of distribution: 0.59 - 2 L/kg	Half-life: Initial: 25-65 h Multiple doses: 12-17 h Metabolism: Metabolized by CYP P450 3A4 into active epoxide metabolite Excretion: 1-3% unchanged in urine	-Induces cytochrome P (CYP)1A2, CYP2B6, CYP2C9/CYP2C19, and CYP3A4, affecting hormonal contraceptives, warfarin, and many other drugs -CBZ metabolism is inhibited by other drugs which inhibit CYP3A4 (*e.g.*, some macrolides, itraconazole or ritonavir)
Ethosuximide	Bioavailability: 93% Volume of distribution: 0.7 L/kg	Half-life: Children: 30 h Adults: 60 h Metabolism: CYP3A4 and CYP2E1 clearance may be non-linear at higher doses Excretion: 12-20% unchanged in urine	-May decrease the serum concentration of valproic acid. -Valproic acid may increase the serum concentration of ethosuximide.
Lamotrigine (LTG)	Bioavailability: 98% Volume of distribution: 0.9-1.3 L/kg	Half-life: Children: 13-27 h Adults: 25-33 h Elderly: 25-43 h Metabolism: >75% metabolized via glucuronidation Excretion: 10% unchanged in urine	-Enzyme-inducing ASMs, rifampin, and oral contraceptives (OCs) decrease LTG level (40+%) -Pregnancy decreases LTG level (~50%-67%) -VPA increases LTG level > 2-fold
Levetiracetam	Bioavailability: 100% Volume of distribution: 0.5-0.7 L/kg	Half-life: 6-8 h Metabolism: 24% of dose hydrolyzed to inactive metabolite Excretion: 66% unchanged in urine	-Levetiracetam can cause depression and agitation. -Doses should be adjusted for renal failure
Oxcarbazepine	Bioavailability: 100% Volume of distribution: 49 L	Half-life: Children: 2-5 years: 4.8-6.7 h 6-12 years: 7.2-9.3 h Adults: 1-5 hrs MHD: 7-20 hrs Metabolism: Oxcarbazepine is extensively metabolized in the liver to its active form 10-monohydroxy metabolite (MHD). MHD undergoes further via glucuronide conjugation. Excretion: <1% unchanged in the urine; 27% as unchanged MHD; 49% as MHD glucuronides; 16% as other metabolites *Clearance*: 2-4 years: increased by 80% compared to adults 4-12 years: increased by 40% compared to adults ≥13: Values approach those for adult clearance	Oxcarbazepine should not be given to patients who developed Stevens-Johnson syndrome while on carbamazepine

▼ **Table 2.** Pharmacokinetic parameters of commonly prescribed antiseizure medications (ASMs) (*continued*).

Drug	Absorption and Distribution	Metabolism and Excretion	Drug Interactions and Special Considerations
Topiramate (TPM)	Bioavailability: 80% Volume of distribution: 0.6-0.8 L/kg	Half-life: 21 hrs Metabolism: Not extensively metabolized. Excretion: 70% unchanged in urine	-Decreased OCs efficacy (TPM >200 mg/d) -Doses should be reduced for renal failure and hemodialysis -Phenytoin and carbamazepine lower TPM concentration - Hypohidrosis and acute glaucoma may occur -Increased risk of kidney stones
Valproic acid (VPA)	Bioavailability: ~90% Volume of distribution: 0.1-0.4 L/kg	Half-life: Newborns (exposed to VPA *in utero*): 30-60 hrs Neonates first week of life: 40-45 hrs Neonates <10 days: 10-67 hrs Children > 2 months: 7-13 hrs Children and adolescents 2-14 years: 9 hrs (range 3.5-20 hrs) Adults: 9-19 hrs Metabolism: 30-50% hepatic via glucuronide conjugation Excretion: <3% unchanged in urine; 30-50% glucuronide conjugate	- Valproic acid may increase serum concentration of carbamazepine active metabolites - Carbamazepine may decrease serum concentration of valproic acid - Valproic acid increases risk of lamotrigine rash - Valproic acid may increase clobazam sedation
Zonisamide (ZNS)	Bioavailability: 100% Volume of distribution: 1.45 L/kg	Half-life: 69 h 27-38 h with enzyme-inducing antiseizure medication, Metabolism: Hepatic metabolism Excretion: 35% unchanged in urine; 65% as metabolites	-Adjust dose in patients with renal impairment -Increased risk of kidney stones -ZNS is a non-arylamide sulfonamide; use with caution in patients with sulfa allergy

Adapted from reference [2].

▼ **Table 3.** Pharmacokinetic parameters of less commonly prescribed antiseizure medications (ASMs).

Drug	Absorption and Distribution	Metabolism and Excretion	Drug Interactions with Other ASMs
Diazepam	Bioavailability: Intranasal: 97% Rectal: 90% Oral: > 90% Volume of distribution: Intranasal: 0.8 - 1.0 L/kg IV: 1.2 L/kg Oral: 1.1 L/kg Rectal 1 L/kg	IV: 33-45 h; desmethyldiazepam 87 h Oral: 44-48 h; desmethyldiazepam 100 h Rectal: 45-46 h; desmethyldiazepam 71-99 h Metabolism: CYP3A4 & CYP2C19 to the active metabolite *N*-desmethyldiazepam, further hydroxylated by CYP3A4 to the active metabolite temazepam and both are further metabolized to oxazepam. Temazepam and oxazepam are largely eliminated by glucuronidation. Excretion: <1% unchanged in urine	-Inhibitors of cytochrome P (CYP) 2C19 and CYP3A4 decrease clearance -Inducers of CYP2C19 and CYP3A4 increase clearance

▼ **Table 3.** Pharmacokinetic parameters of less commonly prescribed antiseizure medications (ASMs) (*continued*).

Drug	Absorption and Distribution	Metabolism and Excretion	Drug Interactions with Other ASMs
Lorazepam	Bioavailability: 90% Volume of distribution: Children: 5 mo - 3 y = 1.62L/kg 3 - 13 y = 1.5L/kg 13 - < 18 y = 1.27L/kg Adult: 1.3 L/kg	Half-Life: Children: 5 mo - 3 y = 15.8 hours 3 - 13 y = 16.9 hours 13 - < 18 y = 17.8 hours Adult: approx. 14 hours Metabolism: Hepatic, rapidly conjugated to inactive glucuronide metabolites Excretion: 12% unchanged in urine	-Reduce the lorazepam dose by 50% with concomitant valproic acid
Phenobarbital	Bioavailability: Neonates and young infants: ~48.9 Adults: 90% Volume of distribution: Neonates: 0.85 ± 0.059 L/kg 2 to 3 months: 0.857 ± 0.089 L/kg 4 to 12 months: 0.57 ± 0.046 L/kg 1 to 5 years: 0.666 ± 0.073 L/kg Adults: 0.61 L/kg	Half-life: ≤10 days of life: 114.2 ± 43 h. 11 to 30 days of life: 73.19 ± 24.17 h. 2 to 3 months: 62.9 ± 5.2 h. 4 to 12 months: 63.2 ± 4.2 h. 1 to 5 years: 68.5 ± 3.2 hours. Adults: ~79 h (range: 53 to 118 hours). Metabolism: Hepatic by oxidation via CYP2C9 and to a lesser extent via CYP2C19 and CYP2E1, and by N-glucosidation Excretion: 25% to 50% unchanged in urine	-Valproic acid increases serum concentrations of phenobarbital
Phenytoin	Bioavailability: Dependent on product and/or salt: Capsules: 70-95% Oral suspension: Neonates reduced by 25% Volume of distribution: Neonates: Premature: 1-1.2 L/kg Full-term: 0.8-0.9 L/kg Infants: 0.7-0.8 L/kg Children: 0.7 L/kg Adults: 0.52-0.78 L/kg	Half-life: Increases with increasing phenytoin concentrations; elimination is not first-order Metabolism: Hepatic through CYP 2C9 and 2C19 Excretion: <5% unchanged in urine	-Induces CYP3A4 (strong) –Decreases carbamazepine, ethosuximide, lamotrigine, oxcarbazepine, sirolimus, topiramate, valproic acid, and zonisamide serum concentrations

▼ **Table 3.** Pharmacokinetic parameters of less commonly prescribed antiseizure medications (ASMs) (*continued*).

Drug	Absorption and Distribution	Metabolism and Excretion	Drug Interactions with Other ASMs
Vigabatrin	Bioavailability: 100% Volume of Distribution: 1.1 L/kg	Half-life: 5 months to 2 yrs: 5.7 hrs 3 to 9 yrs: 6.8 hrs 10-16 yrs: 9.5 hrs Adults: 10.5 hrs Metabolism: Low level of hepatic metabolism Excretion: 80% unchanged in urine	-Vigabatrin decreases phenytoin serum concentrations

Adapted from reference [2].

▼ **Table 4.** Some ASMs can be initiated (as an alternative to the unavailable drug) with the desired therapeutic doses (with no titration up schedule).

Drug	Indications	Starting dose	Maintenance and maximum doses
Levetiracetam	Generalized and focal epilepsies	Loading dose: to achieve a serum concentration of 25 mg/L, use a dose of 15 mg/kg. The loading dose can be given orally. Start levetiracetam with 500 mg/dose, 2 doses per day (10 mg/kg/dose, 2 doses per day, in children).	1000-3000 mg per day in 2 divided doses in adults (maximum dose is 60 mg/kg/day in children).
Valproate	Generalized and focal epilepsies	Start 500 mg/day (10 mg/kg/day in children). A starting dose of 1000 mg/day is not unusual, but may cause nausea and vomiting and may not be tolerated.	Maximum dose is 60 mg/kg/day in children and 3000 mg/day in adults.
Lacosamide	Focal epilepsies and some generalized epilepsies (GTCS)	Start 100 mg/dose (2 mg/dose in children), 2 doses per day.	200-400 mg per day (8-12 mg/kg/day in children), in 2 divided doses.
Phenytoin	Focal epilepsies	Start 15–20 mg/kg PO for non-emergent loading doses in a patient not currently on phenytoin. The loading dose can be divided into two doses separated by 2 hours, but it may be given at once in a single dose; however, a single oral dose of greater than 500 mg has a reduced bioavailability.	Begin maintenance dose (4.5–7 mg/kg/day in 2–3 divided doses, per day) within 12–24 hours (after the loading dose).

GTCS: generalized tonic-clonic seizures. Adapted from reference [2].

Initiating carbamazepine is complicated by its ability to increase its own metabolism. In typical clinical practice, this necessitates titration of the dose to a target maintenance dose over 3-4 weeks. However, evidence suggests that this titration can be done more rapidly over 7-10 days, if needed. To titrate carbamazepine more rapidly, calculate a target maintenance dose of 10-15 mg/kg/day. Administer a daily dose that is 25-30% of the target dose for 2-3 days. Increase the daily dose to 50-60% for the next 2-3 days, then increase the daily dose to 75-90% for the next 2-3 days. After this, the target maintenance daily dose can be used. Dose-related

▼ **Table 5.** A benzodiazepine bridge.

Benzodiazepine	Equivalent oral dose (compared with lorazepam)	Suggested dose as a bridge
Clobazam	10	Adults: 20 mg daily, max. 40 mg/day Children: 0.5 mg/kg/dose twice daily, max. 2 mg/kg/day
Clonazepam	0.25-0.5	Adults: 1-2 mg daily, max. 4 mg/day Children: 0.025-0.05 mg/kg q12h, max. 0.1 mg/kg/q12h
Diazepam	5	Adults: 5-10 mg q8-12h, max. 30-40 mg/day Children: 0.1 mg/kg– 0.15 mg/kg q8h, max. 0.2 mg/kg/q8-12h
Lorazepam	1	Adults: 1-2 mg q8-12h, max. 4 mg/q8-12hr Children: 0.03 mg/kg - 0.05 mg/kg q8h, max 2 mg q8h

Benzodiazepine bridges should not be used in elderly people or in anyone prone to delirium [17].
Adapted from references [2, 17].

adverse effects may be transitory with each dose increase until the maintenance dose is achieved [13, 14]. The most important adverse effects with rapid loading of carbamazepine are allergic reactions ranging from skin rash to Stevens-Johnson syndrome and drug reaction with eosinophilia and systemic symptoms (DRESS). The risk is highest in PWE carrying the HLA-B 1502 genetic marker, which is most prevalent is Asia [15, 16].

To start other ASMs (*e.g.*, lamotrigine, cenobamate, and perampanel, in particular, and also rufinamide, topiramate, and zonisamide) as an alternative to the unavailable drug, a slow up-titration is advised. Therefore, in order to prevent breakthrough seizures or exacerbation of seizures, one should prescribe an available benzodiazepine (*table 5*) along with the desired ASM (the above list) as a bridging drug until the target drug reaches the desired therapeutic dose [17]. A benzodiazepine bridge can be used until ASMs are available or as one titrates to a new medication. When bridging with a benzodiazepine, full dosing should be used while the patient is not on a therapeutic dose of other agents; as therapeutic range of the desired ASM is achieved, the benzodiazepine should be slowly weaned in correlation to the length of time the patient had been on the drug (*i.e.*, if on a benzodiazepine for <two weeks, the drug can be weaned every 2-3 days until cessation over a period of 3-7 days; if on a benzodiazepine for > two weeks, the drug can be weaned every five days by 25% until discontinued).

Generic switches

Switching from brand to generic or between generic ASM products has often been shown to be safe and effective when the generic products have been approved through a rigorous regulatory process and manufactured under Good Manufacturing Practices [18-35]. Usually, this involves the approval and regulation through the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA), or a similar regulatory agency. Many ILAE chapters have endorsed brand to generic or generic to generic switches using products approved and manufactured under these conditions.

For generic products that may not have been approved or manufactured under strong regulatory controls, limited evidence suggests that switches from brand to generic products in this category are also safe and effective [31].

Physicians, pharmacists, and patients need to be vigilant in avoiding drug products that may be sold on the black market. These products may be adulterated, misbranded, or are mislabeled and should be avoided. If possible, availability of these products should be reported to the appropriate authorities and other healthcare professionals, and patients should be notified to avoid them.

Other general suggestions on switching from brand to generic or generic to generic ASMs include [36, 37]:

- Be cautious when switching between various extended-release or controlled-release products. Generic equivalency can be problematic with these products.
- Educate patients and caregivers on the use of generic products. Ensure they understand that even though the tablet or capsule may appear different in size, shape, or color, the product should be equally safe and effective.
- Educate patients and caregivers on any changes in doses or dose frequency.

• Encourage patients or caregivers to report any problems encountered with use of a particular product.

The Medicines and Healthcare Products Regulatory Agency (MHRA) has issued guidance on prescribing ASMs. They advise that certain ASMs should be prescribed using the same version, and that for other ASMs, this is less important [38]. However, in the setting of shortage of ASMs, it is better to utilize available drug products rather than nothing.

Switches between various forms of administration

Switches from extended-release products to immediate-release products are possible. When making these switches, be sure to adjust the dosing interval to accommodate the immediate-release dosage form. Typically, this involves giving the immediate-release product more frequently than the extended-release product. Doses should be based on the total daily dose of the ASM. Calculate the total daily dose of the ASM using the extended-release product. Use this dose as the total daily dose for the immediate-release product and divide the total daily dose into appropriate individual doses for the frequency of dosing. For example, for a total daily dose of an ASM given once a day at 1,000 mg; the individual doses of the immediate-release product should be 500 mg twice daily. Further dose adjustments may be needed to account for bioavailability differences between extended-release and immediate-release products. Switches between delayed-release products can usually be made without difficulty.

Rectal administration of ASMs in emergency situations

When supplies of benzodiazepines (*e.g.*, diazepam, lorazepam, midazolam) or equipment to administer medications intravenously (or via intramuscular, nasal and buccal routes) are not available, rectal administration of some ASMs may be an emergency alternative route for treating serial seizures and status epilepticus. Oxcarbazepine, eslicarbazepine acetate, phenytoin, lorazepam, and midazolam are very poorly absorbed following rectal administration; it is recommended that the rectal route not be used for these medications [39].

Carbamazepine

A dose of 6 mg/kg given as a single dose or divided doses of 400 mg each can be used. Immediate-release oral tablets or oral suspension are used for rectal administration. Extended-release tablets or capsules cannot be used for rectal administration. Dilution of the suspension may be needed to avoid a cathartic effect [40, 41]. At least one study has shown that rectal carbamazepine can be used as alternative long-acting treatment to parenteral ASMs following the termination of cluster seizures or status epilepticus with acute intravenous therapies [40].

Valproic acid

Valproic acid syrup or injection can be given rectally in doses of at least 500 mg. When treating status epilepticus, doses should be the same as intravenous dosing requirements for status epilepticus. Dilution of the syrup may be needed to avoid a cathartic effect. Divided doses may be necessary to avoid large volumes of the drug [42].

Lamotrigine

Lamotrigine may be an alternative to carbamazepine or valproic acid. Studies have used crushed oral tablets mixed in a liquid and administered rectally [43, 44]. The bioavailability of lamotrigine following rectal administration is 50-60% of oral bioavailability. Loading doses of lamotrigine have not been studied [43, 44].

Levetiracetam

Some human and canine data indicate that levetiracetam is absorbed rectally. The intravenous preparation or oral solution can be used. Doses should be the same as intravenous doses used for status epilepticus [45, 46].

Medication considerations in special situations

Infantile epileptic spasms

Diagnosis and treatment should be prompt to optimize longer-term neurodevelopmental outcome. The treatment of choice is combined steroid and vigabatrin therapy once diagnosis has been established [47, 48], unless a diagnosis of tuberous sclerosis is apparent, when vigabatrin alone should suffice [49]. This said, in the absence of vigabatrin therapy, steroids alone can be utilized. No difference has been determined for treatment with oral *vs.* injectable steroids, therefore oral steroids would appear to be safer and easier to administer in emergency crisis situations.
If prednisolone is not available, hydrocortisone can be used. The equivalent ratio to calculate the dose of hydrocortisone to prednisolone is 4:1. Limited evidence

suggests dexamethasone may not be as effective, but could be considered as an alternative in the absence of other steroids [50]. Steroid courses are short for the treatment of spasms, as highlighted above. Vigabatrin is usually continued for longer, but if spasms have resolved, and vigabatrin becomes unavailable, it could be discontinued. Second-line treatments for continuing spasms (and in situations where hormonal treatment or vigabatrin is not available) include benzodiazepine (*e.g.*, clobazam, nitrazepam, clonazepam), topiramate or levetiracetam [51].

Dravet syndrome

Medications likely to have been utilized in a patient with Dravet syndrome include sodium valproate, clobazam, and stiripentol. The latter medication is used in combination with sodium valproate and/or clobazam [52]. Should stiripentol not be available, and consequently discontinued, sodium valproate dose should be increased by one third, and clobazam dose by 50% [53]. Other concomitant ASMs that are metabolized by the cytochrome P-450 system may also need to be increased in dose. Adjustments may need to be made according to patient response and the adverse effects, particularly drowsiness. Cannabidiol may also be utilized (in Europe with clobazam). If an individual is on combination therapy and cannabidiol becomes unavailable clobazam dose should be increased by a quarter [52].
Sodium channel blockers (*e.g.*, phenytoin, carbamazepine, *etc.*) should not be used [54]. This said, if an individual is established and stable on lamotrigine, weaning may not be justified [55].

Developmental and epileptic encephalopathy with spike-wave activation in sleep (previously electrical status epilepticus of slow sleep)

Treatment in the light of acute cognitive deterioration is high-dose steroid treatment [56]. This can be in the form of oral prednisolone (2 mg/kg/day) for 8-12 weeks, followed by a slow wean over six months. Alternatively, hydrocortisone can be used [57]. Safe alternatives are benzodiazepines, specifically clobazam at night. Other medications include valproate, ethosuximide, and lamotrigine.

Lennox Gastaut syndrome

Useful medications include sodium valproate, levetiracetam, clobazam, clonazepam, lamotrigine, zonisamide and topiramate [58]. Cannabidiol may also be utilized (in Europe with clobazam). If an individual is on combination therapy and cannabidiol becomes unavailable, clobazam dose should be increased by a quarter [52]. Although many patients will respond to benzodiazepines, in rare circumstances their tonic seizures may be aggravated and the prescribing physician should be aware of this. Other ASMs that should be avoided in these patients include carbamazepine, oxcarbazepine, phenytoin, and eslicarbazepine acetate [59].

Women of childbearing potential

Certain medications (*e.g.*, valproate) may cause problems in an unborn child (*e.g.*, malformations, neurodevelopmental problems) and therefore should be avoided in women of childbearing age. However, the risks of seizures need to be weighed up against the risk of continuing medication. Levetiracetam and lamotrigine would be considered safer ASM options depending on the type of epilepsy [60]. The serum concentrations of most commonly used ASMs (*e.g.*, levetiracetam and lamotrigine) decrease during pregnancy to various degrees. In women who plan for pregnancy, baseline serum levels of relevant ASMs serve as a reference point to assess subsequent changes during pregnancy and adjust doses accordingly.

The elderly

In utilizing ASMs in the older population, the effect of interaction with concomitant medications in the light of polypharmacy should be considered. Elderly patients may experience increased adverse effects from ASMs compared with younger patients and in general, are likely to have a narrower therapeutic window and greater degree of individual variation with respect to adverse effects. Additionally, consideration should be given to deterioration in renal and hepatic functions. Dose adjustments are necessary depending on the ASM used. For instance, the renal elimination of levetiracetam decreases with increasing age to 50%, when PWE are 65 years or older [61]. Renal function should always be evaluated in older adults before starting ASM that are primarily renally eliminated.

Other complex medical problems

In utilizing ASMs in people with complex medical problems (*e.g.*, high blood pressure, hyperlipidemia, cardiac arrythmias, *etc.*), drug interactions between ASMs and other concomitant medications should be considered. Sodium channel ASMs (*e.g.*, phenytoin, carbamazepine, lacosamide, oxcarbazepine, eslicarbazepine, lamotrigine) should be used cautiously in individuals with cardiac arrhythmias or coronary artery disease [2]. Also, the effects of removal or initiation of enzyme-inducing or -inhibiting drugs

on many ASMs should be considered carefully in PWE.

Conclusion

Sudden withdrawal and discontinuation of ASMs in PWE may have devastating consequences (*e.g.*, ictal injury, status epilepticus, and even death) [62]. During the times of severe ASM shortages, the care and well-being of all PWE should be of paramount concern for all responsible healthcare professionals. This document may help healthcare professionals dealing with PWE during ASM shortages due to emergency situations (*e.g.*, conflicts, disease outbreaks, sudden disruption to international supply chains, *etc.*) to enable them to contemplate appropriate treatment strategies based on the best available evidence and expert opinion. Of course, decision-making regarding treatment strategies and mitigation procedures in this setting is driven by what is best for the patient in consultation with the patient and their caregivers. ■

Key points

- During times of severe ASM shortages, the care and well-being of all PWE should be of paramount concern to healthcare professionals.
- Switching between different ASMs could occasionally be considered as a mitigation procedure.
- Switching from brand to generic or between generic ASM products has often been shown to be safe and effective.
- There are other mitigation procedures to apply in such circumstances.

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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TEST YOURSELF

(1) What pair of antiseizure medications have the potential to be switched from one to another overnight?
A. Oxcarbazepine/carbamazepine
B. Brivaracetam/levetiracetam
C. Clobazam/clonazepam
D. All of the above

(2) Which antiseizure medication cannot be administered rectally in emergency situations?
A. Carbamazepine
B. Oxcarbazepine
C. Valproate
D. Levetiracetam

(3) Some ASMs can be started (as an alternative to an unavailable drug) with the desired therapeutic doses (with no titration-up schedule). These ASMs include:
A. Lacosamide
B. Valproate
C. Levetiracetam
D. All of the above

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.