Title: Treatment strategies in people with epilepsy during times of shortage of antiseizure medications

ILAE Emergency Response (Ukraine) Task Force

1. Introduction

A group of experts [brought together by the International League Against Epilepsy (ILAE)] came together to draft recommendations for managing people with epilepsy (PWE) in times of severe antiseizure medication (ASM) shortages due to emergency situations (e.g., disasters, conflicts, disease outbreaks, sudden disruption to international supply chains, etc. Every effort has been made to base these suggestions on direct published literature or extrapolations from basic information about ASMs. Actual published literature in this area is limited and at times, assumptions were required by the experts. 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 (AEs). These risks have to be taken into consideration and the patient should be informed and reassured 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.

2. Mitigation procedures during times of shortage of ASMs

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

2.A. **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. In case of need, the two medications can be directly switched instantly considering the above mentioned ratios

2.B. **Eslicarbazepine acetate/ oxcarbazepine/ carbamazepine**: The overnight transition between oxcarbazepine and eslicarbazepine acetate (or vice versa) in a 1:1 ratio is generally well

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

2.C. **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, you can switch between these two drugs instantly considering the above mentioned ratio.

2.D. **Brivaracetam/ levetiracetam**: 50 mg of brivaracetam could be replaced by 1000 mg levetiracetam, 100 mg of brivaracetam by 2000 mg levetiracetam and 200 mg of brivaracetam by 3000 mg levetiracetam. In case of need, these two drugs can be interchanged instantly considering the above mentioned ratio.

2.E **Primidone/Phenobarbitol**: Primidone is is metabolized to phenobarbitol and phenylethylmalonamide (PEMA). PEMA is also known to have anti-epileptic properties. Around 24% primidone is converted to phenobarbitol; in light of the additional anti-epileptic properties of PEMA, a switch of primidone to phenobarbitol can be made 1:4 but consideration given to an additional dose in the first 24 hours.

2.F. **Other ASMs**: For many 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:

a. Some ASMs (as an alternative to the unavailable drug) can be started with the desired therapeutic doses. In such circumstances consider at least one overlapping dose. These ASMs include:

a.1. **Levetiracetam** (in both generalized and focal epilepsies): Switching to levetiracetam can be done relatively quickly and a loading dose can be used to rapidly achieve good serum concentrations. To achieve a serum concentration of 25 mg/L, use a dose of 15 mg/kg. The loading dose can be given orally. The typical maintenance dose for the patient should be started 12 hours after

administering the loading dose. Start levetiracetam with 500 mg/dose, 2 doses per day (10 mg/kg/dose, 2 doses per day, in children). Usual maintenance dose is 1000-3000 mg per day in 2 divided doses in adults (maximum dose is 60 mg/kg/day in children).

a.2. **Valproate** (in both generalized and focal epilepsies): start 500 mg/day (10 mg/kg/day in children). Maximum dose is 40 mg/kg/day in children and 3000 mg/day in adults.

a.3. **Lacosamide** (in focal epilepsies and some generalized epilepsies): start 100 mg/dose (4 mg/dose in children), 2 doses per day. Usual maintenance dose is 200-400 mg per day (8-12 mg/kg/day in children), in 2 divided doses.

a.4. **Phenytoin** (only in 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 have a reduced bioavailability. Following the completion of oral loading, begin maintenance dose (4.5–7 mg/kg/day in 2–3 divided doses per day) within 12–24 hours. Remember that phenytoin follows zero-order pharmacokinetics, so small dose changes in maintenance doses may result in large changes in concentrations and increased dose-related adverse effects.

b. 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 adverse effects may be transitory with each dose increase until the maintenance dose is achieved. The most important AEs with rapid loading 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. 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 titration-up is advised. Therefore, in order to prevent breakthrough seizures or exacerbation of seizures, one should prescribe an available benzodiazepine (Table 2) along with the desired ASM (the above list) as a bridging drug until the target drug reaches the desired therapeutic dose. 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 off in correlation to the length of time the patient had been on the drug (i.e., if on a benzodiazepine for < 2 weeks, can wean every 2-3 days until off over 3-7-day period; if on a benzodiazepine for > 2weeks, can wean every 5 days by 25% until discontinued).

3. 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. 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 safe and effective. Any decision regarding use of these products should be made with the best interests of the patient in mind.

Physicians, pharmacists, and patients need to be vigilant in avoiding drug products that may be sold on the black market. The products may be adulterated, misbranded, or 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 switch from brand to generic or generic to generic ASMs include:

1. Avoid switches between various extended-release or controlled-release products. Generic equivalency can be problematic with these products.
2. 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 with 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. (e.g., A total daily dose of an ASM given once a day is 1000 mg. The immediate-release product needs to be given twice daily. Individual doses of the immediate-release product should be 500 mg twice daily.) and the dose frequency of the immediate-release product adjusted in accordance with manufacturer recommendations.
3. Switches between delayed-release products can usually be made without difficulty.
4. 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.
5. Educate patients and caregivers on any changes in doses or dose frequency.
6. 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 with the same version, and that for other ASMs this is less important. However, in the setting of shortage of ASMs, it is better to have any drugs that are available rather than nothing.

4. Rectal administration of ASMs in emergency situations

When supplies of benzodiazepines (e.g., diazepam, lorazepam) 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. 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.

4.1. 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 is used for rectal administration. Extended-release tablets or capsules cannot be used for rectal preparations. Dilution of the suspension may be needed to avoid a cathartic effect. At least one study showed that status epilepticus can be treated with rectally administered carbamazepine. If the patient is being initiated on carbamazepine or it has been >10 days since the last dose of carbamazepine, maintenance carbamazepine dosing can be started using the titration schedule noted above.

4.2. 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 consistent with 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.

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

4.4. 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.

5. Medication considerations in special situations

5.1. Vigabatrin

Vigabatrin is used specifically in the treatment of infantile epileptic spasms; although, it is also utilized in rare circumstances for refractory focal onset seizures, specifically where they are the result of Tuberous Sclerosis Complex (TSC).

Infantile Epileptic Spasms are a seizure type with onset in the first year of life, regardless of underlying cause. Patients often present with a developmental plateau, with the onset of clusters of flexor or extensor spasms often related to the sleep wake cycle, most commonly seen on

awakening. Often there is a profoundly abnormal EEG of high amplitude disorganized spike and slow wave activity, also known as hypsarrhythmia. Although EEG is highly recommended when diagnosis is suspected, lack of access to EEG should not delay treatment. Diagnosis and treatment should be prompt to optimize longer term neurodevelopmental outcome. Treatment of choice is combined steroid and vigabatrin therapy once diagnosis has been established, unless a diagnosis of Tuberous Sclerosis is apparent, when vigabatrin alone should suffice. This said, in the absence of vigabatrin therapy, steroids alone can be utilized. No difference has been determined in the treatment with oral *vs.* injectable steroids, therefore oral steroids would appear to be safer and easier to administer in emergency crisis situations.

In the initial treatment of new diagnosis infantile spasms, *s*tart prednisolone treatment at a dosage of 10 mg 4 times daily. If spasms stop within 7 days, continue at the same dosage for 14 days in total then wean over 15 days:

- reduce to 10 mg 3 times daily for 5 days
- then, 10 mg twice daily for 5 days
- then, 10 mg once daily for 5 days and then stop.

If spasms continue after 7 days, increase the dosage to 20 mg 3 times daily for a further 7 days then wean over 15 days:

- reduce to 10 mg 4 times daily for 5 days
- then, 10 mg twice daily for 5 days
- then, 10 mg once daily for 5 days and then stop.

If prednisolone is not available, hydrocortisone can be used. The equivalent ratio in calculating 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. Second line treatments (and in situations where hormonal treatment or vigabatrin is absolutely not available) include benzodiazepine (e.g., clobazam, nitrazepam, clonazepam), topiramate or levetiracetam.

Use of vigabatrin for focal seizures: In the absence of vigabatrin, consider switching to another appropriate ASM (Table 1).

5.1. Dravet syndrome

Dravet syndrome is an early onset complex developmental and epileptic encephalopathy. 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. Should stiripentol not be available, and consequently discontinued, sodium valproate dose should be increased by one third, and clobazam by 50%. 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.

IN ALL CIRCUMSTANCES USE OF SODIUM CHANNEL BLOCKERS (E.G., PHENYTOIN, CARBAMAZEPINE, OXCARBAZEPINE, ESLICARBAZEPINE ACETATE, AND LAMOTRIGINE) SHOULD NOT BE USED IN VIEW OF THE RISK OF AGGRAVATION OF SEIZURES. This said, if an individual is established and stable on lamotrigine a wean may not be justified.

5.2. Developmental & Epileptic Encephalopathy with spike wave activation in sleep (previously electrical status epilepticus of slow sleep)

This is a very specific syndrome, in which overt seizures may be infrequent, but deterioration in cognitive or language functions are associated with the development of continuous spike wave activity during slow sleep. The diagnosis cannot be made without sleep as well as awake EEG recordings. Treatment in the light of acute cognitive deterioration is high dose steroid treatment. This can be in the form of oral prednisolone (2mg/kg/day) for 8-12 weeks, followed by a slow wean over 6 months. Alternatively, hydrocortisone can be used. Safe alternatives are benzodiazepines, specifically clobazam at night. Other medications include ethosuximide and lamotrigine.

5.3. Lennox Gastaut syndrome

Individuals with this diagnosis are likely to have a complex epilepsy, characterized by multiple seizure types including tonic seizures, drop (atonic/tonic) seizures, atypical absences, and frequent episodes of status epilepticus, particularly non-convulsive status epilepticus. Useful medications include sodium valproate, levetiracetam, clobazam, clonazepam, lamotrigine,

zonisamide and topiramate. 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 one quarter. Although, many patients will respond to benzodiazepines, in rare circumstances their tonic seizures may be aggravated. Other ASMs that should be avoided in these patients include carbamazepine, oxcarbazepine, phenytoin, and eslicarbazepine acetate.

5.4. Pregnant women

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 child bearing 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 dependent on the type of epilepsy.

5.5. Elderly

In utilizing ASMs in the older population, the effect of interaction with concomitant medications in the light of polypharmacy needs to 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. Renal function should always be evaluated in older adults before starting ASM that are primarily renally eliminated.

5.6. Other complex medical problems

In utilizing ASMs in people with complex medical problems (e.g., high blood pressure, hyperlipidemia, etc.), the effect of interaction with those medical problems and also with concomitant medications in the light of polypharmacy needs to be considered.

Table 1. Choice of antiseizure medications 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
Dravet syndrome	*Valproate*, stiripentol, cannabidiol, topiramate, benzodiazepines, phenobarbital, ethosuximide, levetiracetam **Carbamazepine, phenytoin, vigabatrin, and lamotrigine are contraindicated.**
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 **In mitochondrial disorders, valproate is contraindicated.**
Developmental & epileptic encephalopathy with spike wave activation in sleep (formerly, Landau-Kleffner syndrome)	*Valproic acid, diazepam*, 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 choice in men and *levetiracetam* is the drug of choice in women. 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, felbamate, phenobarbital, zonisamide
Tonic seizures	Valproate, topiramate, rufinamide, lamotrigine, clobazam, levetiracetam, cannabidiol, felbamate, phenobarbital, zonisamide

* First-choice drug is given in italics.

Adapted from: Asadi-Pooya AA, Sperling MR. Antiepileptic Drugs: A Clinician's Manual. Second Edition. New York, Oxford University Press; 2016.

Table 2. A benzodiazepine bridge

Benzodiazepine	**Equivalent oral dose (compared with lorazepam)**	**The 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.