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To Whom it May Concern:

This letter is meant to provide **clinician guidance for treatment of seizures in Angelman syndrome** based on "Seizure treatment in Angelman syndrome: A case series from the Angelman Syndrome Clinic at Massachusetts General Hospital" (Shaaya et al, 2016; PMID: 27206232), "A multidisciplinary approach and consensus statement to establish standards of care for Angelman syndrome" (Duis et al, 2022; PMID: 35150089), and expert review.

**Note:** This document includes general guidance meant to support clinician decision-making, not to replace professional judgement or evaluation of the patient. Each patient is unique and may not respond to the typical medications used in Angelman syndrome. To request consultation with a neurologist who specializes in the management of seizures in Angelman syndrome, please email **clinics@angelman.org.**

**Angelman syndrome (AS)** is a rare neurogenetic condition typically caused by a multigene deletion on the maternal copy of chromosome 15q11.2-13.1. Angelman syndrome may also be caused by a mutation in the UBE3A gene, imprinting center defect, or paternal uniparental disomy.

**Individuals with Angelman syndrome are at increased risk of seizures, particularly in the setting of febrile illnesses in childhood.**

As many as 80-95% of children with AS due to a deletion will develop seizures by 3 years old. Parents and caregivers may be the first to recognize clinical changes in their children. Children with Angelman syndrome often present with atonic or drop seizures but can have generalized tonic-clonic, focal, or other seizure types as well.

If there are **prolonged seizures** or the **patient with AS is not returning to baseline** between brief seizures, benzodiazepines should be considered first line to stop seizure activity in AS. Depending on clinical status, oral versus IV or intranasal preparations can be utilized and in the typically recommended weight-based dosing for children and standard dosing for adults.

**Outpatient management of new onset seizures:**
Levetiracetam (Keppra), Clobazam (Onfi), or Clonazepam (Klonopin) should be considered as a first line therapy. Low Glycemic Index diet could also be considered.

- Parents should be encouraged to monitor for side effects of anti-seizure medications in their child.
- Regular clinical laboratory testing may need to be monitored depending on the choice of antiseizure medication
- For first line medications the follow side effects should be noted.

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  - Levetiracetam may cause increased irritability.
  - Higher doses of clobazam may negatively affect alertness, drooling, and balance.
  - Higher dose of Clonazepam may affect alertness, drooling, and balance

- If seizures are not controlled on initial first line medication, then consider switching to monotherapy of one of the other medications.
- Low or very low dose clonazepam (0.125 to 0.25 mg twice a day) should be considered as a first line therapy for brief atonic or myoclonic type seizures. Patients who do not respond to clobazam may respond to clonazepam.

**Other considerations:**

- If first line therapies do not work, then consider Valproate (aka depakote, depakene, valproic acid) next as monotherapy
  - Valproate may cause tremor, decreased balance, and/or regression of motor skills. These symptoms may improve when the patient is tapered off valproate.
  - It may be beneficial to assess selenium and zinc levels in children on Valproate, especially with hair loss.

**Seizure rescue medications:**

All patients with Angelman syndrome should be provided with a prescription for seizure rescue medications after their first seizure.

- Seizure rescue medications can include rectal diazepam (Diastat), intranasal diazepam (Valtoco approved for 6yo and older), intranasal midazolam (any form and Nayzilam is approved for 12yo and older).
- In some countries, buccal midazolam products are available for rescue therapy.

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## General recommendations for the management of generalized epilepsy, convulsive status epilepticus, and non-convulsive status epilepticus

***Adapted figure from Duis et al, 2022***

### Generalized Epilepsy

EEG for difficult to control seizures on first tier medication or if needed to characterize events

**First Tier:**
Consider broad spectrum AED (clobazam or livitiracetam or LGIT as intial therapy. If persistent seizures on LGIT, add broad spectrum AED

**Second Tier:**
Consider seizure type and consider epidiolex, lamotrigine, topiramate

If LGIT not started initially, consider LGIT or ketogenic diet, especially if two medications fail

Consider use of vagal nerve stimulator if refractory to medication and diet. Resective surgery is not recommended

### Convulsive Status Epilepticus

Follow hospital protocol

**First Tier:**
Benzodiazepines (e.g. lorazepam, clonazepam, diazepam). EEG should help guide treatment

**Second Tier:**
Levetiracetam, if available. Otherwise consider fosphenytoin, lacosamide, depacon, or phenobarbital per hospital protocol

**Third Tier:**
Continuous midazolam infusion or as per hospital protocol

### Non-Convulsive Status Epilepticus

**First Tier:**
Diazepam (may require a continued long taper if short taper is ineffective)

**Second Tier:**
Steriod taper

Adjunctive therapiers; clobazam, ethosuximide*, lamotrigine, topiramate

Consider IV medications including steroids, levetiracetam, lacosamide, depacon, and if available acetazolamide, could be used in difficult to control NCSE

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