Medications for epilepsy management in the ambulatory setting

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TCH APP Conference 2019
Disclosure

- I have no conflicts of interest to disclose

- In some instances medications will be presented with off-label use to treat specific seizure types. This will be noted in italics.
Objectives

1. Identify the difference between seizures and epilepsy

2. Describe common types of epileptic seizures in pediatrics

3. Discuss steps to manage epilepsy in pediatrics

4. Outline initial medication therapy to treat common types of epilepsy in pediatrics
Definitions

*Seizure:* a sudden stereotyped episode that presents with a change in motor activity, sensation, behavior, and/or consciousness caused by abnormal electrical discharge in the brain

*Epilepsy:* Any of the following
  - ≥ 2 unprovoked seizures occurring within 24 hours
  - 1 unprovoked seizure and a recurrence risk
  - Diagnosis of an epilepsy syndrome

*Status Epilepticus:* disease process resulting in prolonged seizures > 5 minutes

*Resolved epilepsy* occurs for patients who had an age-dependent epilepsy syndrome and are past the age of said syndrome or patients who are seizure free for the last 10 years with no medication for at least 5 years
Seizure pathophysiology

*Excessive excitation or disordered inhibition of a collection of cortical neurons

Contributors to synchronous hyperexcitability:

- Changes in distribution, type, number, and biophysical properties of ion channels in neuronal membranes
- Biochemical alteration of receptors
- Modulation of second messaging systems and gene expression
- Change in extracellular ion concentrations
- Variation in neurotransmitter uptake and metabolism in glial cells
- Alteration in ratio and function of inhibitory circuits
Provoked Seizures

- Infection
- Trauma
- Metabolic abnormality
- Toxic exposure
- Fever
- Stroke
In 2015, 1.2% of the U.S. population had active epilepsy. This accounts for about 3 million adults and 470,000 children nationwide.
Seizure Evaluation

To establish diagnosis and categorize seizure type:

- Obtain a detailed description of event(s)
- Perform general physical exam and neurologic exam
- Obtain an EEG

Identify possible etiology & determine likelihood of recurrence:

- Obtain a detailed description of event(s)
- Collect past and recent medical history
- Ask about family history
- Collect appropriate labs
  - Genetic testing, autoimmune marker
  - Imaging if appropriate
Knowledge Check #1

Do all patients who present with a seizure have epilepsy?
### ILAE 2017 Classification of Seizure Types Expanded Version

<table>
<thead>
<tr>
<th>Focal Onset</th>
<th>Generalized Onset</th>
<th>Unknown Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aware</strong></td>
<td><strong>Motor</strong></td>
<td><strong>Motor</strong></td>
</tr>
<tr>
<td>Impaired Awareness</td>
<td>tonic-clonic</td>
<td>tonic-clonic</td>
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<tr>
<td></td>
<td>clonic</td>
<td>clonic</td>
</tr>
<tr>
<td></td>
<td>tonic</td>
<td>myoclonic</td>
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<tr>
<td></td>
<td>myoclonic-tonic-clonic</td>
<td>epileptic spasms</td>
</tr>
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<td></td>
<td>myoclonic-atonic</td>
<td>atonic</td>
</tr>
<tr>
<td></td>
<td>epileptic spasms</td>
<td></td>
</tr>
<tr>
<td><strong>Non-Motor Onset</strong></td>
<td><strong>Non-Motor (absence)</strong></td>
<td><strong>Non-Motor (absence)</strong></td>
</tr>
<tr>
<td></td>
<td>typical</td>
<td>behavior arrest</td>
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<tr>
<td></td>
<td>atypical</td>
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<tr>
<td></td>
<td>myoclonic</td>
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<tr>
<td></td>
<td>eyelid myoclonia</td>
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<tr>
<td></td>
<td>focal to bilateral tonic-clonic</td>
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</tbody>
</table>

1. Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms
2. Degree of awareness usually is not specified
3. Due to inadequate information or inability to place in other categories

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**1. Onset**

**2. Awareness**

**3. Other features**
ILAE 2017 Classification of Seizure Types Basic Version

- **Focal Onset**
  - Aware
  - Impaired Awareness
- **Generalized Onset**
  - Motor
    - Tonic-clonic
    - Other motor
  - Non-Motor (Absence)
- **Unknown Onset**
  - Motor
    - Tonic-clonic
    - Other motor
  - Non-Motor
- **Unclassified**
  - focal to bilateral tonic-clonic
ILAE Classification of the Epilepsies

Co-morbidities

Seizure types
- Focal onset
- Generalized onset
- Unknown onset

Etiology
- Structural
- Genetic
- Infectious
- Metabolic
- Immune
- Unknown

Epilepsy types
- Focal
- Generalized
- Combined Generalized & Focal
- Unknown

Epilepsy Syndromes

Childhood Absence Epilepsy

* Onset: between 2 and 12 years old

* Between age 8 and 12, juvenile versus childhood absence epilepsy is based on seizure frequency

* Presentation: behavioral arrest and unresponsiveness

* Brief: average 10 seconds

* Frequent: multiple daily

* Intellect and neurological exam often normal

* Neuroimaging often normal and/or not required

* Typical absence seizures remit in 80%

AAP. Types of Seizures and Common Epilepsy Syndromes in Children. ILAE. Epilepsy diagnosis.org.
Childhood Epilepsy with Central Temporal Spikes

* Also known as Benign Epilepsy of Childhood with Central-Temporal Spikes (BECCTS) or Benign Rolandic Epilepsy (BRE)

* Onset: between 3 and 14 years

* Presentation: focal seizures with motor symptoms involving face and arm
  * Mainly nocturnal seizures
  * Can secondarily generalize
  * Often infrequent occurrence

* Intellect and neurological exam often normal

* Can have language based learning disorders

* Patients almost always experience remission by mid to late adolescence

Juvenile Myoclonic Epilepsy (JME)

* Onset: between 8 and 25 years
* Presentation:
  * Generalized convulsive seizures occur in almost all patients (90%)
    * Frequently main symptom
  * Myoclonus: mandatory for diagnosis
  * Frequently early morning/photonic stimulation induced
  * Co-occurrence of absence seizures in 15-40%

* Intellect and neurological exam often normal
* JME usually persists for life

AAP. Types of Seizures and Common Epilepsy Syndromes in Children. ILAE. Epilepsy diagnosis.org.
Infantile spasms

* Occurrence about 1 in 4,000-6,000 live births
* Onset: between 4-8 months old
* 90% begin before 12 months
* Presentation: 3 major groups of seizures
  * **Flexor**: flexion of neck, trunk, arms, legs
  * **Extensor**: mainly extensor muscle contractions resulting in abrupt extension of neck and trunk
  * Mixed flexor-extensor
* 85% children with intellectual disability

* Earlier treatment improves prognosis
* Etiology varied:
  * Genetic, prenatal, perinatal, postnatal or unknown causes

* **West Syndrome** is a triad of:
  * Infantile spasms
  * Interictal EEG with hypsarrythmia
  * Intellectual disability

AAP. Types of Seizures and Common Epilepsy Syndromes in Children.
ILAE. Epilepsy diagnosis.org.
Lennox-Gastaut Syndrome (LGS)

* Mixed seizure disorder
* Tonic seizures from sleep are characteristic
* Onset: between 1 and 8 years
* EEG: Diffuse slow spike-and-wave and paroxysm of fast activity on EEG
* Neuroimaging depending on etiology
* Structural abnormalities common cause
* Developmental stagnation or regression common after seizure onset

Knowledge Check #2

True or false: Every patient diagnosed with epilepsy will be diagnosed with an epilepsy syndrome?
Treatment Plan

- Safety Precautions
- Rescue Medication
- Preventative Medication
Seizure First Aid

What to do in the event of a seizure

1. STAY with the person and start timing the seizure. Remain calm and check for medical ID.
2. Keep the person SAFE. Move or guide away from harmful objects.
3. Turn the person onto their SIDE if they are not awake and aware. Don’t block airway, put something small and soft under the head, loosen tight clothes around neck.
4. Do NOT put anything in their mouth. Don’t give water, pills or food until the person is awake.
5. Do NOT restrain.
6. STAY with them until they are awake and alert after the seizure. Most seizures end in a few minutes.

Call 911:

- Seizure lasts longer than 5 minutes
- Repeated seizures
- Trouble breathing
- Seizure occurs in water
- Patient injured, pregnant, or sick
- Patient not returning to baseline health
- First seizure

Epilepsy Foundation. 2018.
Safety

First Aid
Make a seizure safety plan
Give instructions on when to call EMS

Environment
Home
School
Driving

Activities
Water
Sports
Other physical activity

Psychosocial
Increased risk mental health & learning disorders
## Rescue Medication

For prolonged or recurrent seizures

<table>
<thead>
<tr>
<th>Use when:</th>
<th>Non-oral route:</th>
<th>Implement seizure safety plan and follow up per provider instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Multiple seizures within a short time or seizure lasting more than 5 minutes*</td>
<td>• Rectal diazepam</td>
<td></td>
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</tbody>
</table>

| Indication | Treat status epilepticus in children and adults for initial outpatient therapy |
| Mechanism | GABA-A receptor agonist, enhances inhibitory effect of endogenous GABA |
| Dosing | 2-5 years: 0.5 mg/kg  
 6-11 years: 0.3 mg/kg  
 ≥12 years and Adults: 0.2 mg/kg  
 Round up to the nearest 2.5 mg increment, max: 20 mg/dose |
| Adverse Effects (AE) | Sedation, dizziness, depression, fatigue, motor and cognitive impairment, tolerance/withdrawal with prolonged use |
| Monitoring | Seizure resolution, sedation |
| Formulations | Twin pack of 2.5mg, 10mg, 20mg; Rectal gel, available as 5mg/mL (delivers doses of 5, 7.5, 10mg) (other formulations: injection, solution, tablet) |
| Drug-drug interactions (DDI) | CNS depressants, Inhibitors of CYP2C19 (cimetidine) and CYP3A4 (azoles) can decrease clearance; inducers of 2C19 (rifampin) and 3A4 (carbamazepine, phenobarbital, phenytoin, dexamethasone) can increase elimination |
| Clinical Pearls | C-IV controlled substance; Contraindicated in narrow angle glaucoma |
Disposal:
- Pull plunger all the way up until completely removed from syringe body
- Point over sink or toilet
- Replace plunger into syringe body and push plunger until it stops
- Flush toilet or rinse sink until gel no longer visible
- Discard all used material in garbage can in safe space away from children
Case 1: SJ

SJ is a 5 y.o. female with NKDA who presents to your clinic for follow up and referral to neurology after having a brief witnessed seizure at school yesterday. Mom notes they used to have diazepam rectal at home after her febrile seizure but it was disposed of after expiring.

Height: 117 cm  Weight: 21.5 kg

PMH: Febrile seizure x 1 at years old ; seasonal allergic rhinitis

Current medication(s): cetirizine 5 mg by mouth once daily as needed for allergy symptoms

1. What diagnostic tests or referrals would you initiate?
2. What questions would you ask?
3. How might you prescribe rectal diazepam?
Seizure Prevention Medication

Initiate daily preventative medication by specialist confirming epilepsy diagnosis with:
- Occurrence of 2nd seizure
- 1st unprovoked seizure with ↑ risk for recurrence
- Neurologic deficit present
- EEG with clear epileptiform activity
- Patient/family consider risk unacceptable
- Brain imaging with structural abnormality

NICE, 2012.
AAP. Medication Management of Epilepsy.
General Medication Considerations

**Starting Medication**
Based on epilepsy type/syndrome, age, comorbidities, side effect profile, access, lifestyle, patient/family preference

**Changing Medication**
Usually for adverse effects/unable to tolerate, lack of efficacy

**Adding Medication**
Events continue despite optimal dose first line medication; only if attempts at monotherapy not resulting in seizure freedom

**Stopping Medication**
Patient/provider decision, based on risk recurrence, long term control

NICE, 2012.
AAP. Medication Management of Epilepsy.
## Absence seizures

<table>
<thead>
<tr>
<th>First Line</th>
<th>Alternatives</th>
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</thead>
<tbody>
<tr>
<td>Ethosuximide</td>
<td>Valproic acid</td>
</tr>
<tr>
<td></td>
<td>Lamotrigine</td>
</tr>
</tbody>
</table>

*Antiepileptic drugs (AED) to avoid as they may aggravate absence seizures:* Carbamazepine, vigabatrin, gabapentin, tiagabine, phenytoin, phenobarbital

NICE, 2012.
AAP. Medication Management of Epilepsy.
# Ethosuximide
(Zarontin®)

## Indication
Absence seizures

## Mechanism
Affects low threshold, slow, T-Ca\(^{2+}\) thalamic currents

## Dosing
- **3 to 6 years**: start 250 mg orally daily; usual optimal daily dose: 20 mg/kg/day divided BID or TID
- **≥6 years and Adolescents**: start 250 mg BID; usual optimal daily dose: 20 mg/kg/day divided BID or TID
- Max: lesser of 60 mg/kg/day or 2,000 mg/day

## AE
N/V, abdominal pain, anorexia, weight loss, diarrhea, sedation, dizziness, ataxia, ↓ WBC, sleep disturbance, gum hypertrophy, tongue swelling, change in mood (hyperactivity, depression, irritability, psychosis)

### Warnings/precautions:
SJS, DRESS, pancytopenia, eosinophilia, lupus

## Monitoring
CBC with differential, platelets, liver and renal function, UA, mood, rash; serum ethosuximide concentration: 40-100 mcg/mL

## Formulations
Oral capsule 250mg, oral solution 250mg/5mL

## DDI
CNS depressants, CYP3A4 substrate

## Clinical Pearls
Use caution with renal or hepatic disease; can increase tonic-clonic seizures if used as monotherapy for mixed seizure disorder
## Valproic acid
**(Depacon, Depakote®)**

### Indication
- **Focal**, tonic-clonic, **absence**, mixed seizure disorder
- *(most formulations FDA approved ≥10 years)*

### Mechanism
- Enhances GABA activity, Inhibits voltage-dependent Na⁺ and T-type Ca²⁺ channels

### Dosing
- General: start 10-15 mg/kg/day in 1-3 divided doses; maintenance 30-60mg/kg/day in 2-3 divided doses

### AE
- Hyperammonemia +/- encephalopathy, thrombocytopenia, coagulopathy, hypothermia, abdominal pain, alopecia, anxiety, ataxia, asthenia, constipation, depression, diarrhea, double vision, dizziness, dyspnea, emotional lability, fever, infection, HA, insomnia, N/A, nystagmus, edema, pharyngitis, rash, sedation, abnormal thinking, tinnitus, tremor, weight change
- Warnings: hepatotoxicity, hypersensitivity, pancreatitis

### Monitoring
- Liver enzymes (baseline and within 1st 6 months), bilirubin, serum ammonia, CBC with platelets, PT/PTT, mental status/motor and cognitive function, mood, serum valproic acid level: 50-100+ mcg/mL

### Formulations
- Capsule (250mg), delayed release sprinkle capsule (125mg), IV solution (100mg/mL), oral solution (250mg/5mL), delayed release tablet (125, 250, 500 mg), (Age 10+: extended release tablet (250, 500mg))

### DDI
- MANY: CNS depressants, estrogens, phenytoin, salicylates; Metabolized by CYP 3A4

### Clinical Pearls
- **Contraindications**: hepatic disease, POLG mutation, urea cycle disorders, pregnancy
- *Boxed warning for hepatotoxicity, patients with mitochondrial disease, fetal risk, pancreatitis*
- Valproic acid and derivatives not preferred in patients <2 due to increased risk hepatotoxicity
# Lamotrigine
(Lamictal®)

<table>
<thead>
<tr>
<th><strong>Indication</strong></th>
<th>LGS, primary generalized tonic-clonic seizures, <strong>focal</strong> seizures, adjunct therapy, <strong>absence</strong> seizures <em>(Not FDA approved)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Enhances Na⁺ channel rapid inactivation; inhibits Ca²⁺ channel; activates postsynaptic HCN channels</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Based on age, weight, indication, <strong>concomitant medications</strong> <em>(Immediate release FDA approved age ≥2 years for focal, LGS, primary TCS, extended release ≥ 13 years)</em></td>
</tr>
<tr>
<td><strong>AE</strong></td>
<td>Dizziness, headache, diplopia, ataxia, N/V, somnolence, insomnia in high doses, aseptic meningitis</td>
</tr>
<tr>
<td><strong>Warnings/precautions:</strong></td>
<td>Rash, SJS/TEN, HLH <em>(8 cases since 1994)</em></td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Hypersensitivity <em>(RASH)</em>, CBC with differential, liver and renal functions, mood changes/suicidality, serum level of lamotrigine: 4-20 mcg/mL; serum levels of concurrent anticonvulsants</td>
</tr>
<tr>
<td><strong>Formulations</strong></td>
<td>Oral tablet <em>(25, 100, 150, 200 mg)</em>, chewable tablet <em>(5, 25mg)</em>, ODT <em>(25, 50, 100, 200 mg)</em>, extended release tablet <em>(25, 50, 100, 200, 250, 300 mg)</em></td>
</tr>
<tr>
<td><strong>DDI</strong></td>
<td>CNS depressants, Enzyme inducing AEDs, valproic acid, rifampin, oral contraceptives</td>
</tr>
<tr>
<td><strong>Clinical Pearls</strong></td>
<td>Also indicated for bipolar disorder/mood stability; avoid with sodium channel defects <em>(Dravet syndrome)</em> as can worsen epilepsy</td>
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</tbody>
</table>
Case 2: VM

VM is a 7 y.o. female with a history of constipation, who presents to Neurology clinic with her mother after referral from her PCP. Patient presents due to with episodes of “distractedness” noticed by her family and teachers for the past 7 months. Episodes last 5-10 seconds and have increased in frequency to 3-4 times daily. V will often ask what happened after episode which can be accompanied by humming and eye movements. She continues doing well academically in the 1st grade but does report feeling anxious at school sometimes with rapid breathing and feeling like she wants her mother.

Ht: 136 cm Wt: 41.2 kg NKDA

Meds: Polyethylene glycol: mix 17g with at least 4 ox of water or juice and drink immediately once daily as needed for constipation

In clinic, Neurologist noted patient had 2 very brief episodes of behavioral arrest. With a provocation challenge of over 1 minute of hyperventilation, patient had a 5 second episode of multiple automatisms and behavior arrest. Patient was diagnosed with childhood absence epilepsy (CAE).

Plan: The natural history of CAE, seizure precautions, and seizure first aid were discussed with patient’s mother, an EEG was ordered with plans to start patient on ethosuximide 250 mg by mouth once daily at bedtime for one week and then increase to 250 mg by mouth twice daily pending result.
Case 2: VM Questions

1. What supports the diagnosis and initial therapy (if started) for VM?

2. How would you counsel V and her parents on medication administration?

3. How would you monitor for safety? Efficacy?

4. Is patient on the maximum dose?
# Childhood Epilepsy with Central Temporal Spikes

<table>
<thead>
<tr>
<th>First Line</th>
<th>Alternatives/Adjunct</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Levetiracetam</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Phenytoin</td>
</tr>
</tbody>
</table>
## Carbamazepine
*(Carbatrol, Tegretol®)*

<table>
<thead>
<tr>
<th>Indication</th>
<th><strong>Focal</strong> and generalized <strong>tonic clonic seizures</strong>, mixed seizure types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Enhances Na⁺ channel rapid inactivation; block L-type Ca²⁺ channel</td>
</tr>
</tbody>
</table>
| Dosing     | - <6 years: start 10-20 mg/kg/day divided 2-3 times daily as IR tablets or 4 times daily as suspension; Maximum recommended daily dose: 35 mg/kg/day  
  - 6-12 years: start 100 mg twice daily or 50 mg of suspension 4 times daily Maximum recommended daily dose: 1000 mg/day (age 6-15)  
  - Adolescents: Initial: 200 mg twice daily; Maximum recommended daily dose: 1200 mg/day (age > 15) |
| AE         | Sedation, N/V, blurred vision, hyponatremia, lethargy, dizziness, headache, hypersensitivity, diplopia, ataxia, low WBC count, decreased T3, T4, increased LFTs  
  **Warnings/precautions:** SJS & TEN, aplastic anemia, agranulocytosis, DRESS |
| Monitoring | Serum carbamazepine level: 4-12 mcg/mL unless concomitant anticonvulsant; HLAB*1502 genotype for some, CBC, serum iron, LFTs, ophthalmic exam, UA, Lipid panel, TFTs, serum sodium |
| Formulations | Extended release capsule, oral suspension, tablet, chewable tablet, extended release tablet  
  *suspension and 12 hour capsule FDA approved in all ages |
| DDI        | MANY (Induces CYP1A2, 2B6, 2C9/19 and 3A4); Contraindicated with nefazadone, boceprevir, delavirdine, MAOIs |
| Clinical Pearls | Indications for bipolar disorder, chronic pain syndromes (trigeminal neuralgia); don’t use for absence seizure |

## Oxcarbazepine

**Trileptal®**

### Indication
Focal seizures, monotherapy or adjunctive therapy

### Mechanism
Enhances Na\(^+\) channel rapid inactivation; block Ca\(^{2+}\) channel; enhances K\(^+\) conductance

### Dosing
- **2-16 years**: start 8-10 mg/kg/day in 2 divided doses, maximum start 300 mg BID; maintenance/max dose depends on weight (*FDA approved as monotherapy for age ≥ 4; adjunct ≥ 2 years*)
- **≥17 years**: 300 mg twice daily for week 1 then add no more than 300 mg BID each week (range 1200 mg – 2400 mg)

### AE
Dizziness, ataxia, headache, URI, N/V, diarrhea or constipation, dyspepsia, nervousness, hyponatremia

**Warnings/precautions:** SJS & TEN

### Monitoring
 serum level: 10-35 mcg/mL as MHD, HLAB*1502 genotype for some, efficacy, CNS depression, CBC, serum sodium

### Formulations
Suspension (300mg/5mL), tablet (150, 300, 600 mg), 24 hour extended release tablet (150, 300, 600mg)

### DDI
CNS depressants; Cyp3A4 metabolite; Induces CYP3A4 (reduces estrogen level at higher doses); inhibits CYP2C19

### Clinical Pearls
IR and XR formulations are NOT bioequivalent and NOT interchangeable on a mg/mg basis, dose adjust for severe renal failure; TID dosing can improve tolerability
# Gabapentin  
*(Neurontin®)*

<table>
<thead>
<tr>
<th><strong>Indication</strong></th>
<th>Focal seizures with or w/o secondary generalization, adjunct therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Binds presynaptic $\alpha_2$-$\delta$ subunit of Ca$^{2+}$ channel to modulate Ca$^{2+}$ current &amp; $\downarrow$ glutamate, NE, and substance P release</td>
</tr>
</tbody>
</table>
| **Dosing** | **3-12 years:** start 10 to 15 mg/kg/day divided into 3 doses daily  
**Usual maintenance:**  
**Age 3 to 4 years:** 40 mg/kg/day divided into 3 doses daily  
**5-12 years:** 25 to 35 mg/kg/day divided into 3 doses daily  
**≥12:** start 300 mg 3 times daily; usual maintenance dose: 900 to 1,800 mg/day divided into 3 doses daily; doses up to 2,400 mg/day divided into 3 doses daily have been well tolerated long-term |
| **AE** | Sedation, ataxia, dizziness, diplopia, nystagmus, peripheral edema, fever, viral infection, N/V, tremor  
**Warnings/precautions:** DRESS, anaphylaxis, angioedema, neuropsychiatric changed in children 3-12 years |
| **Monitoring** | Renal function, weight, behavior, signs and symptoms of suicidality, serum gabapentin level: 4-8.5 mcg/mL |
| **Formulations** | Oral capsule (100mg, 300mg, 400mg), oral solution 250 mg/5mL, oral tablet (600mg, 800mg) |
| **DDI** | CNS depressants |
| **Clinical Pearls** | Also indicated for neuropathic pain; dose adjustment required for renal insufficiency |
Levetiracetam
(Keppra®)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Myoclonic seizures with JME <em>(FDA approved in ages 12+)</em>; focal seizures <em>(as adjunct approved age ≥1 month)</em>, tonic-clonic seizures <em>(FDA approved in ages 6+)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Inhibits synaptic vesicle SV2A protein; partially inhibits N-type Ca(^{2+}) currents</td>
</tr>
</tbody>
</table>
| Dosing     | **1 to <6 months:** Start 7 mg/kg/dose twice daily; in clinical trials mean daily dose 35 mg/kg/day  
**≥6 months and Children <4 years:** Start 10 mg/kg/dose twice daily; in clinical trials mean daily dose 47 mg/kg/day  
**≥4 years <16 years:** Start 10 mg/kg/dose twice daily; maximum of 30 mg/kg/dose twice daily or total 3,000 mg/day; in clinical trials mean daily dose 44 mg/kg/day; older pediatric patients and adults *(eg, weight >50 kg):* Initial fixed dose of 500 mg twice daily suggested |
| AE         | Somnolence, fatigue, asthenia, dizziness, depression, behavioral change *(aggression, irritability)*, ataxia, infection, anemia, leukopenia, thrombocytopenia, diastolic blood pressure change in patients <4 years  
**Warnings/precautions:** SI, SJS & TEN, pancytopenia, rhabdomyolysis, angioedema |
| Monitoring | Efficacy, CNS depression, psychiatric and behavioral symptoms, diastolic BP in patients <4; serum levetiracetam level: 20-50 mcg/mL |
| Formulations | IV solution *(regular and PF)*, oral solution *(100 mg/mL)*, tablet, orally disintegrating tablet *(ODT)*, 24 hour extended release tablet *(oral range from 250-1000 mg tablets)* |
| DDI        | CNS depressants |
| Clinical Pearls | Dose adjustment required with renal impairment |
## Lacosamide
*(Vimpat®)*

### Indication

**Focal** seizure, as adjunct or monotherapy

### Mechanism

Enhances Na⁺ channel slow inactivation

### Dosing

- **≥4 -17 years:**
  - 11 to <30 kg: start 1 mg/kg/dose by mouth twice daily; maintenance: 3 to 6 mg/kg/dose twice daily
  - 30 to <50 kg: start 1 mg/kg/dose by mouth twice daily; maintenance: 2 to 4 mg/kg/dose twice daily
  - ≥50 kg: start 50 mg by mouth twice daily; Maintenance: **Monotherapy:** 150 to 200 mg twice daily; **Adjunctive therapy:** 100 to 200 mg twice daily

### AE

Dizziness, ataxia, diplopia, headache, nausea, prolonged PR interval, increase risk cardiac arrhythmias

### Warnings/precautions:

- Hypersensitivity, suicidal ideation

### Monitoring

- EKG (in select patients), hepatic and renal function, mood, heart rate and blood pressure (IV), serum lacosamide level: 4-12 mcg/mL, vision (especially with changes)

### Formulations

- IV solution (*FDA approved age ≥17 years* - 200mg/20mL), oral solution (10mg/mL – contains aspartame, methylparaben, propylene glycol- strawberry), oral tablet (50, 100, 150, 200 mg)

### DDI

- Strong Cyp3A4 inhibitors, Class III antiarrhythmics, bradycardia causing medications, lidocaine, orlistat, QT-prolonging Class IA and IC antiarrhythmics

### Clinical Pearls

- Not recommended with severe hepatic impairment, use caution with renal impairment
# Phenytoin
(Dilantin®)

## Indication
- **Focal** seizures, status epilepticus, generalized **tonic-clonic** seizures, seizure prophylaxis w/ neurosurgery

## Mechanism
- Enhances rapid inactivation of Na\(^+\) channels

## Dosing
- **Children:** start 5mg/kg/day divided BID
- **Adults:** 300 mg/day divided BID or TID
- *Individualize doses based on clinical response and serum concentrations with adjustments no more than every 7 days*

## AE
- Nystagmus, ataxia, dysarthria, cognitive slowing, gingival hyperplasia, rash, hypertrichosis, lymphadenopathy, pseudolymphoma, hepatotoxicity, thrombocytopenia, leukopenia, pancytopenia, Long term use: peripheral neuropathy, vitamin D deficiency, osteoporosis

## Warnings/precautions:
- SJS/allergic reaction

## Monitoring
- CBC with differential, liver function, suicidality, serum phenytoin concentration: 10-20 mcg/mL (~10% free)

## Formulations
- Oral capsule as sodium (30, 100, 200, 300mg), injection solution (sodium salt – 50mg/mL), oral suspension (125mg/mL), chewable tablet (50mg)

## DDI
- Vitamin D/calcium; MANY interactions; major substrate of CYP2C19, 2C9 and induces CYP1A2, 2B6, 3A4, PGP UGT1A1

## Clinical Pearls
- Caution conversion between formulations: phenytoin base contains ~8% more drug than phenytoin sodium; special kinetics, Steady state in 5-10 days
# Zonisamide

**(Zonegran®)**

| **Indication** | Focal seizures-adjunct age >16 years; *off label use/studied for: generalized epilepsies (generalized tonic-clonic, absence seizures, infantile spasms, myoclonic epilepsies, LGS)* |
| **Mechanism** | Enhances rapid inactivation at Na⁺ channels, ↓ low-threshold T-type Ca²⁺ current; binds GABA_A ionophore; carbonic anhydrase inhibitor |
| **Dosing** | ≤16 years: Start 1-2 mg/kg/day in 2 divided doses, usual dose 5-8 mg/kg/day; maximum 12 mg/kg/day > 16 years: Start 100 mg by mouth every day, increase by 100 mg every 2 weeks Usual maintenance 400-600mg/day as 1-2 doses |
| **AE** | Kidney stones, rash, sedation, anorexia, weight loss, dizziness, ataxia, agitation, psychosis, irritability, speech or language disturbance, depression **Warnings/precautions:** SJS/TEN, DRESS, ↓ WBC, anemia, oligohydrosis and hyperthermia in children, hyperchloremic metabolic acidosis |
| **Monitoring** | Efficacy, CBC, chemistry, serum zonisamide level: 10-40 mcg/mL |
| **Formulations** | Capsule (25, 50, 100mg) |
| **DDI** | CNS depressants; carbamazepine, phenobarbital, phenytoin, valproic acid; carbonic anhydrase inhibitors |
| **Clinical Pearls** | Do not crush, chew, or break capsule |
Case 3: FS

FS is a 5 year old female with no significant past medical history who presents to Neurology clinic for post hospital follow up of newly diagnosed partial seizures. Patient admitted to hospital for second seizure within one month. Mother reported second seizure at night lasted minutes with lip smacking and right eye deviation. First seizure lasted 2-3 minutes with right arm and leg tonic-clonic rhythmic shaking with eye deviations and stopped without pharmacologic intervention. Patient recently discharged on oxcarbazepine suspension as below. In clinic patient with normal neurologic exam and no reported adverse effects from therapy.

Ht: 111 cm  Wt: 20.4 kg  NKDA

Meds: oxcarbazepine 300 mg/5mL oral suspension: give 3.2 mL by mouth 2 times daily; diazepam 10 mg rectal gel: insert 5 mg in the rectum once as needed for seizure lasting more than 5 minutes for one dose.

Hospital EEG: asymmetric focal slowing from left posterior–parieto occipital region suggesting underlying focal abnormality or postictal. No epileptiform discharges.

Hospital MRI brain: asymmetric abnormal signal within the left hippocampus and subtle abnormal signal in adjacent mesial temporal lobe without significant associated volume loss. Appearance not specific and could be the cause or sequela of seizure activity.

Plan:
- Adjust Trileptal to 4 ml BID (25 mg/kg/day, adjusted for ease of dosing)
- Diastat 10 mg rectal gel: insert 7.5 mg rectally as needed for seizure > 5 minutes
- MD discussed the risks, benefits and alternatives of plan with family. General epilepsy education and precautions reviewed. Encouraged to exercise judgement of risk during any activity, and recommended avoidance of or close supervision in any situation where sudden loss of awareness or a fall may be harmful to the patient or others. Also discussed first-aid management of seizures, and indications for an emergency room visit or a 911 call. Emphasized the importance of periodic follow-up visits, and compliance with the medications. A possible interaction of the anti-epileptic medication with other medications should also be discussed with the prescribing physician whenever new medication is started.
- Instructed family to call if symptoms worsen or with any questions or concerns in the interim.
Case 3: FS Questions

1. Can you identify the 3 steps of epilepsy management in this patient’s case?

2. Do medication doses appear appropriate?

3. What follow up labs would you obtain?

4. Major drug-drug interactions to look out for?
<table>
<thead>
<tr>
<th>First Line</th>
<th>Alternatives or Adjunct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levetiracetam <em>(FDA approved in ages 12</em>)</td>
<td>Topiramate</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Zonisamide</td>
</tr>
<tr>
<td>Valproic acid</td>
<td></td>
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</tbody>
</table>
Topiramate
(Topamax, Qudexy, Trokendi®)

**Indication**
- Focal seizures initial or adjunct therapy, LGS adjuct, **generalized tonic-clonic** initial or adjunct, *infantile spasms* (non FDA)

**Mechanism**
- Inhibits Na⁺ channels, kainite receptors and carbonic anhydrase, enhances GABA$_A$

**Dosing**
- Varies based on formulation and indication
- **2 to 16 years** for partial or LGS immediate release formulation: start 1 to 3 mg/kg/day (max 25 mg/dose) nightly, usual maintenance 5-9 mg/kg/day in 2 divided doses
- In dose response studies in adults dose > 400mg/day not shown to have efficacy

**AE**
- Paresthesia, anorexia, weight loss, speech and cognitive disturbance, sedation, dizziness, anxiety, abnormal vision, fever, diarrhea, nausea, abdominal pain, URI
- **Warning/precaution:** acute myopia, glaucoma, visual field defects, hyperammonemia, metabolic acidosis, hyperthermia, kidney stones

**Monitoring**
- Efficacy, renal function, electrolytes including periodic bicarbonate levels, eye exam, signs/symptoms of suicidality, serum topiramate level: 7-30 mcg/mL

**Formulations**
- 24 hour capsule sprinkle (25, 50, 100, 150, 200 mg), 24 hour capsule (25, 50, 100), sprinkle capsule (15, 25mg), oral tablet (25, 50, 100, 200mg)

**DDI**
- CNS depressants, phenytoin and carbamazepine, lithium, oral contraceptives, carbonic anhydrase inhibitors

**Clinical Pearls**
- Dose adjustment for renal failure, also used for migraine prophylaxis (age 12 and up); *XR formulations approved for different ages based on seizure type treating; Qudexy and Trokendi not bioequivalent
## Infantile spasms

<table>
<thead>
<tr>
<th>First Line</th>
<th>Alternatives, Refractory, and/or Adjunct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenocorticotropic hormone (ACTH)</td>
<td>Valproic acid</td>
</tr>
<tr>
<td>Vigabatrin (1st line for tuberous sclerosis)</td>
<td>Topiramate</td>
</tr>
<tr>
<td></td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Indication</td>
<td>Infantile spasms</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Stimulates adrenal secretion of cortisol, corticosterone, aldosterone and other steroids</td>
</tr>
</tbody>
</table>
| Dosing           | *Multiple dosing strategies have been evaluated  
Manufacturer labeling infants and children 2 and under: 75 IU/m²/dose administered IM twice daily for 2 weeks followed by a 2 week taper |
| AE               | Infections, adrenal insufficiency, HTN, Cushing syndrome, salt/water retention, \( \downarrow K^+ \), alkalosis, gastric ulcers, bleeding, weight gain, bowel perforation, behavior or mood disturbances  
**Contraindicated:** congenital or other infections, recent surgery, uncontrolled hypertension, sensitivity to porcine proteins, live or live-attenuated vaccines, primary adrenal insufficiency, heart failure |
<p>| Monitoring       | Efficacy, blood pressure, serum glucose, potassium, calcium, intraocular pressure (for therapy &gt;6 weeks), linear growth, HPA suppression |
| Formulations     | 80 units/mL injection gel (5mL) |
| DDI              | Corticosteroids, immunosuppressant therapy, vaccines *MANY – consult reference |
| Clinical Pearls  | $$, Only available through specialty pharmacies, dose calculator available through manufacturer with training materials for patients coming soon; consider GI prophylaxis with H2 blocker |</p>
<table>
<thead>
<tr>
<th>Indication</th>
<th>Infantile spasms, Adjunct for refractory complex partial seizures <em>(FDA approved age ≥ 10 years)</em> <em>in patients where potential benefits &gt; potential risk of vision loss</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Increases GABA through irreversibly inhibiting GABA-Transaminase</td>
</tr>
<tr>
<td>Dosing</td>
<td><strong>Infantile spasms (1-24 months):</strong> Start 25mg/kg BID; max 150 mg/kg/day <strong>Adjunct for refractory complex partial seizures age 10 and up:</strong> If weight 25-60 kg and age 10-16 years: start 250 mg BID; recommended maintenance 1,000mg BID; to taper decrease by 1/3 daily dose weekly -If weight over 60 kg or age over 16: start 500 mg BID; recommended maintenance 1,500 mg BID; to taper decrease dose by 1,000 mg/day weekly</td>
</tr>
<tr>
<td>AE</td>
<td>Sedation, tremor, nystagmus, blurred vision, decrease memory, increased weight, ataxia, arthralgia, tremor, diplopia, aggression, URI, anemia, neuropathy, edema <strong>Black Box Warning:</strong> vision loss</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Ophthalmic exam (baseline, 1 month, then every 3 months), sedation, efficacy, Hgb/HCT, renal function, weight, suicidality, neurotoxicity, peripheral neuropathy, edema</td>
</tr>
<tr>
<td>Formulations</td>
<td>500 mg tablet; 500 mg oral powder packet for solution</td>
</tr>
<tr>
<td>DDI</td>
<td>CNS depressants, phenytoin, carbamazepine</td>
</tr>
<tr>
<td>Clinical Pearls</td>
<td>REMS program; dose adjust in renal impairment; can precluding use of markers for hepatic injury; can increase amino acids in urine leading to false positive for rare genetic metabolic disorders</td>
</tr>
<tr>
<td>First Line</td>
<td>Alternatives, Refractory, and/or Adjunct</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Cannabidiol</td>
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<tr>
<td>Topiramate</td>
<td>Clobazam</td>
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<tr>
<td>Valproic acid</td>
<td>Felbamate</td>
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<tr>
<td></td>
<td>Rufinamide</td>
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</tbody>
</table>
| **Cannabidiol**  
<table>
<thead>
<tr>
<th><strong>(Epidiolex®)</strong></th>
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<tbody>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
</tr>
</tbody>
</table>
| **Dosing** | ≥2 years: Start at 2.5 mg/kg/dose twice daily, may increase in 1 week to maintenance dose of 5 mg/kg/dose twice daily  
- If additional seizure control needed, may increase weekly by 2.5 mg/kg/dose twice daily  
- Maximum: 20 mg/kg/day |
| **AE** | Somnolence/sedation, elevated LFTs, decreased appetite/weight loss, diarrhea, fatigue, malaise, rash, insomnia, sleep disorder, infections, irritability, hypersensitivity (angioedema, erythema, pruritus)  
**Warnings/precautions:** hypersensitivity, CNS depression, |
| **Monitoring** | Assess ALT, AST, and total bilirubin prior to initiating treatment, with dose changes or the addition of or changes in hepatotoxic medications and at 1, 3, 6 months of therapy |
| **Formulations** | Oral solution 100mg/mL (100 mL bottle strawberry flavor, contains alcohol, sesame oil) |
| **DDI** | CNS depressants, some hepatic enzyme interactions including CYP2C19, valproate, clobazam |
| **Clinical Pearls** | C-V controlled substance; High fat/high calorie meals ↑ extent of absorption; artisanal formulation of cannabidiol are not biopharmaceutically equivalent and shouldn’t be substituted; adjust for hepatic impairment |
# Clobazam
*(Onfi; Sympazan®)*

<table>
<thead>
<tr>
<th><strong>Indication</strong></th>
<th>LGS as adjunct; <em>monotherapy/adjunct for generalized or focal seizures</em> <em>(off-label)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td><strong>GABA</strong>&lt;sub&gt;A&lt;/sub&gt; receptor agonist, binds between α and γ subunits <em>(1,5 benzo)</em></td>
</tr>
</tbody>
</table>
| **Dosing**     | **Age ≥ 2 years:** ≤30 kg: Start 5 mg once daily for ≥1 week, can then increase to 5 mg twice daily for ≥1 week, then increase to 10 mg twice daily thereafter (max: 20 mg/day)  
>30 kg: Start 5 mg twice daily for ≥1 week, may then increase to 10 mg twice daily for ≥1 week, then increase to 20 mg twice daily thereafter (max: 40 mg/day) |
| **AE**         | Sedation, fever, infection *(URI/UTI/pneumonia)*, drooling, constipation, insomnia, irritability, depression, dependence/withdrawal effects, vomiting, ataxia  
**Warnings/precautions:** Rash, SJS and TEN |
| **Monitoring** | Respiratory and mental status; CBC; liver and renal function, serum clobazam level: 0.25-0.75 mcg/mL |
| **Formulations** | Oral film *(5, 10, 20 mg)*; Tablets *(10, 20 mg)*; oral suspension *(2.5mg/mL – berry flavor ; use provided syringe and adapter for dosing)* |
| **DDI**        | CNS depressants *(especially opiates)*, some CYP450 based interactions- major substrate of CYP2C19, inhibits CYP2D6 weakly, induced CYP3A4 weakly |
| **Clinical Pearls** | CIV controlled substance; Taper off by 5-10 mg/week if stopping ; different dose titration in hepatic impairment and CYP2C19 poor metabolizers |

Clobazam. Lexi-Drugs.
# Felbamate

**Felbatol®**

<table>
<thead>
<tr>
<th><strong>Indication</strong></th>
<th><strong>Focal</strong> seizures, monotherapy or adjunct (FDA approved age ≥14); <strong>adjunct in LGS</strong> (age 2-14 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Enhances Na⁺ channel rapid inactivation; blocks Ca²⁺ channel; inhibits NMDA receptor, potentiates GABA&lt;sub&gt;A&lt;/sub&gt; conductance</td>
</tr>
</tbody>
</table>
| **Dosing**    | **Children:** Start 15 mg/kg/day in 3 or 4 divided doses, increase weekly by 15mg/kg/day to max of lesser of 45mg/kg/day or 3,600 mg per day  
**Age ≥14:** Start 1,200 mg/day in 3 or 4 divided doses; titration depends on monotherapy or adjunctive therapy, maximum 3,600 mg/day |
| **AE**        | Headache, insomnia, N/V, abdominal pain, anorexia, weight loss, facial edema, anxiety, acne, rash, constipation, diarrhea, ↑SGPT, hypophosphatemia, rhinitis, infection, somnolence, ataxia, dizziness, tremor  
**Warnings/precautions:** Aplastic anemia, hepatic failure (>6 cases/75,000 patients/year) **Contraindicated** with history blood dyscrasia or hepatic dysfunction, hypersensitivity to felbamate or carbamates |
| **Monitoring**| Efficacy, CBC with differential and platelets & LFTs (before, frequently during, and after treatment), mood change/suicidality, serum felbamate level: 60-100 mcg/mL |
| **Formulations** | Suspension 600mg/5mL ; tablets (400mg, 600 mg) |
| **DDI**       | CNS depressants, CYP3A4 inducers/inhibitors (decreases progestin in contraceptives), dose adjustment of many concomitant AED required on initiation |
| **Clinical Pearls** | Only for patients who respond inadequately to alternatives with benefits > risk, renal dose adjust |
# Rufinamide
(Banzel®)

<table>
<thead>
<tr>
<th><strong>Indication</strong></th>
<th><strong>Adjunct in LGS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Enhances Na(^+) channel rapid inactivation</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>≥1 and &lt;17 years: start 10 mg/kg/day in 2 equally divided doses; target daily dose of 45 mg/kg/day in 2 doses; maximum daily dose: 3,200 mg/day</td>
</tr>
<tr>
<td></td>
<td>≥17 years: start 400 to 800 mg/day in 2 equally divided doses; increase by 400-800 mg every other day to target/maximum daily dose of 3,200 mg/day in 2 doses (unknown efficacy in lower doses)</td>
</tr>
<tr>
<td><strong>AE</strong></td>
<td>Leukopenia, shortened QT interval, headache, N/V, dizziness, fatigue, irritability, emotional disturbance</td>
</tr>
<tr>
<td><strong>Warnings/precautions:</strong></td>
<td>Rash, DRESS, status epilepticus; contraindicated in familial short QT syndrome</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Efficacy, CBC, signs of suicidality, consider ECG (especially with other agents which shorten QT interval), serum rufinamide level: 5-48 mcg/mL</td>
</tr>
<tr>
<td><strong>Formulations</strong></td>
<td>Suspension (40mg/mL- contains propylene glycol); tablets (200, 400 mg)</td>
</tr>
<tr>
<td><strong>DDI</strong></td>
<td>Weak inducer of CYP3A4 (estradiol, other AEDs), CNS depressants</td>
</tr>
<tr>
<td><strong>Clinical Pearls</strong></td>
<td>Initial dose adjust with concomitant valproate use; not recommended in severe liver failure</td>
</tr>
</tbody>
</table>
Knowledge Check # 3

Which of the following medications is not indicated at any age as initial or adjunct/alternative therapy in LGS?

A. Banzel®
B. HP Acthar®
C. Onfi®
D. Topamax®
Additional Considerations

* Monotherapy versus polytherapy
* Long term monitoring
* Medication interactions
* When to stop medication
* Women’s health
Questions?
References


References

References


