Drug Selection and Initiation/Titration

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Learning Objectives:

1. Review the principles of anti-seizure drug selection based on seizure type(s), epilepsy type, syndrome and etiology (if known).
2. Discuss other considerations in anti-seizure drug selection, such as age, comorbidity, and social factors.
3. Review the recommended initiation dose and titration rates for the most commonly used anti-seizure drugs, and the factors that may influence these.

The treatment of epilepsy should ideally follow a firm diagnosis by clinical history, supported by electroencephalography and brain imaging. It is optimal to have seizure types classified, and if possible the epilepsy syndrome and or etiology diagnosed. At present the treatment of epilepsy usually begins with pharmacotherapy using one anti-seizure drug that is effective against the diagnosed seizure types (see Table 1) and is also safe and well tolerated. The medication chosen should not have unfavorable interactions with the patient’s other medications. At a minimum, the chosen medication should not be unfavorable to comorbid conditions such as depression or migraine, but ideally the chosen medication is also effective against comorbid conditions. At present, the epilepsy etiology does not play a major role in drug selection, with the exception of a handful of conditions. For example, autosomal dominant nocturnal frontal lobe epilepsy responds best to carbamazepine and oxcarbazepine; generalized epilepsy due to glucose transporter deficiency responds best to the ketogenic diet; Dravet syndrome (severe myoclonic epilepsy of infancy) is aggravated by drugs that are classic sodium channel blockers; and epilepsies of autoimmune origin respond to immune therapies.

Initial therapy - focal seizures

Almost all anti-seizure drugs are effective against focal seizures, the main exception being ethosuximide which is a narrow spectrum drug against generalized absence seizures. Ideally, the first drug chosen should have undergone a successful initial monotherapy trial. Comparative trials of anti-seizure drugs in
newly diagnosed epilepsy have greatly affected clinical practice. For example, among older antiseizure
drugs the large trial comparing carbamazepine, phenytoin, phenobarbital, and primidone favored
carbamazepine and phenytoin due to their superior tolerability. However, in much of the developing
world, phenobarbital is still very widely used because it is the most affordable anti-seizure medication. A
later trial comparing carbamazepine and valproate favored carbamazepine due to greater efficacy
against focal seizures not evolving to bilateral tonic-clonic activity and due to superior tolerability.
However, most old anti-seizure drugs have disadvantages related to pharmacokinetic interactions. In
particular, carbamazepine, phenytoin, and phenobarbital are potent hepatic enzyme inducers, reducing
the efficacy of other drugs metabolized by the liver, as well as endogenous hormones. Valproate is a
potent enzyme inhibitor that reduces the clearance of some medications. Several new anti-seizure drugs
have pharmacokinetic advantages with less potential for adverse interactions. In particular, lamotrigine,
topiramate, oxcarbazepine, levetiracetam, zonisamide, lacosamide, and eslicarbazepine acetate can be
considered for initial monotherapy (even though lamotrigine is FDA approved for conversion to
monotherapy and levetiracetam and zonisamide do not have FDA indication for monotherapy).
Gabapentin could also be considered, but it also has no FDA monotherapy indication and its adjunctive
efficacy was relatively low. A large community-based study of time to treatment failure found
lamotrigine significantly better than immediate release carbamazepine, gabapentin, and topiramate.
Lamotrigine also had a nonsignificant advantage over oxcarbazepine.

If rapid onset of action is required, for example due to severe seizures recurring over a short period of
time, then lamotrigine may not be appropriate since it requires a slow titration. Oxcarbazepine,
levetiracetam, lacosamide, and eslicarbazepine acetate can be started at an effective dose. Topiramate
also requires a slow titration. As a result of cognitive adverse effects, it is generally not a drug of first
choice. However, if there is a comorbidity of migraine it may be chosen due to its efficacy in migraine
prevention.

In the absence of urgency, it is a generally preferable to initiate an anti-seizure medication at a low dose
and titrate it slowly to the minimal effective dose, even when the drug can be started at a larger dose.
For a patient with frequent seizures, the target dose can be the minimum effective dose. However, for
patients with infrequent seizures, the medication has to be titrated to an intermediate effective dose.

**Initial therapy- Generalized seizures**

Unlike the case with focal seizures, many anti-seizure drugs are not effective against generalized onset
seizures. Only three drugs have received Class I investigation as initial monotherapy for generalized
absence seizures. Ethosuximide and valproate were clearly more effective than lamotrigine, and ethosuximide had less adverse neuropsychological effects than valproate. However, ethosuximide has a very narrow spectrum of efficacy against generalized absence seizures only. When other generalized seizure types coexist, valproate is preferable due to its broad spectrum of efficacy. Zonisamide has not been formally tested against generalized absence seizures in a Class I trial. However, several Class IV studies suggested efficacy against absence seizures, and one of its mechanisms of action is blocking T calcium currents, a mechanism predictive of efficacy against generalized absence seizures.

The only anti-seizure drug with an FDA indication against generalized myoclonic seizures based on a Class I trial is levetiracetam as adjunctive therapy. However, there is a large body of evidence suggesting that valproate is efficacious against this seizure type. Either valproate or levetiracetam can be used as initial monotherapy. Other anti-seizure drugs with a broad spectrum of efficacy, such as zonisamide, topiramate, lamotrigine, and benzodiazepines could be considered. Lamotrigine can occasionally aggravate generalized myoclonic seizures in some patients, although it is effective in others. Brivaracetam is likely to have a similar efficacy profile to levetiracetam, though it has undergone only limited trials against generalized seizures. It should be noted that a number of anti-seizure medications can aggravate myoclonic and absence seizures, and even cause them to appear de novo. The list includes carbamazepine, oxcarbazepine, phenytoin, gabapentin, pregabalin, tiagabine, and vigabatrin, all of them anti-seizure medications with a narrow spectrum of efficacy against focal seizures.

More anti-seizure drugs are efficacious against generalized tonic-clonic seizures than against generalized absence and myoclonic seizures. However, no Class I trials have investigated drugs as initial monotherapy. In a large community-based study comparing valproate, topiramate, and lamotrigine in patients with idiopathic generalized epilepsy, valproate was better than both lamotrigine and topiramate for the time to treatment failure. In this study the basis for treatment failure was either poor tolerability or poor efficacy, primarily against generalized tonic-clonic seizures. Valproate should remain a drug of first choice for men, but due to its teratogenicity it should not be the first drug of choice for women of childbearing potential. Lamotrigine, levetiracetam, or zonisamide should be used first. Topiramate is associated with increased risk of oral clefts in exposed infants and should also not be a drug of first choice in women of childbearing potential. Perampanel was recently approved for treatment of generalized tonic-clonic seizures, but the trials resulting in approval used adjunctive therapy.

Other generalized seizure types, such as generalized tonic and generalized atonic seizures have been studied mostly as part of Lennox-Gastaut syndrome. In general, they should be treated with a broad-spectrum agent such as valproate, lamotrigine, topiramate, zonisamide, or levetiracetam. Felbamate,
rufinamide, and clobazam have indications for adjunctive therapy of Lennox-Gastaut syndrome, but are not usually considered initial treatment options.

**Other considerations in the choice of the first anti-seizure drug**

There are numerous individual considerations that should influence the choice of the first anti-seizure medication. Some comorbidities could make certain anti-seizure drugs less appropriate. For example, history of mood disorder may make levetiracetam less desirable; hyponatremia is a relative contraindication to oxcarbazepine; zonisamide and topiramate should be avoided if there is history of kidney stones. In the presence of obesity valproate is less desirable because it is associated with weight gain, and drugs that are associated with weight loss or are weight neutral are preferred. The presence of insomnia can make lamotrigine less desirable.

Safety and tolerability of anti-seizure drugs may be a function of age or gender. Certain unfavorable adverse effects may be more likely in children or in the elderly. For example, valproate-induced hepatic failure is more likely in children younger than 2 years of age. Hyponatremia from oxcarbazepine is uncommon in children and more likely to occur in the elderly. In a large comparative study in seniors, lamotrigine and gabapentin were better tolerated than immediate-release carbamazepine. In women of childbearing potential, valproate should be avoided due to its teratogenicity. For those on oral contraceptives, anti-seizure drugs that reduce the efficacy of the oral contraceptives may need to be avoided. The list includes the older enzyme inducing anti-seizure drugs carbamazepine, phenytoin, and phenobarbital, as well as the newer oxcarbazepine, eslicarbazepine acetate, and topiramate (> 200 mg). The risk of adverse drug interactions may not be an issue in young individuals not taking other medications, but is a concern in seniors who are often taking medications for comorbidities, and anti-seizure drugs that have no interactions are preferable in the older age group.

The pharmacokinetics of certain anti-seizure drugs can also make them more or less desirable in certain settings. Anti-seizure drugs that require a lengthy titration process may not be appropriate when there is a need to treat rapidly due to frequent or severe seizures. Pharmacokinetics also become important in the presence of organ failure. In an individual with liver failure it is best to choose an anti-seizure drug that is not metabolized by the liver, or at least not extensively metabolized by the liver.
Considerations after the first anti-seizure drug fails.

When the first medication fails due to poor tolerability, the appropriate management is to switch to an alternative monotherapy medication. The reason for failure of the first medication should influence the choice of the next drug, with an effort to avoid similar adverse experiences. For example, if the first medication produced excessive sleepiness or cognitive dysfunction, then a less sedating medication should be chosen. If the first anti-seizure medication was well-tolerated but not effective, either alternative monotherapy or adjunctive therapy can be chosen. If the first medication was totally ineffective, alternative monotherapy is most appropriate. Alternative monotherapy would also be preferable if it is difficult for the patient to keep up with two medications, if there are financial limitations to taking two medications, if it is desirable to limit medications due to pregnancy or potential pregnancy, or if the patient is already on multiple medications for other comorbidities. On the other hand, adjunctive therapy would be appropriate if the first medication was partially effective. If the initial seizures were severe, the patient may be concerned about the risk of seizure recurrence upon withdrawing the first anti-seizure medication.

Regardless of whether alternative monotherapy or adjunctive therapy is chosen, the second anti-seizure medication should be effective against the seizure types present, and should not have the potential for seizure exacerbation (for example while carbamazepine may be effective against generalized tonic-clonic seizures, it may exacerbate absence and myoclonic seizures in a patient with idiopathic generalized epilepsy). The second anti-seizure drug should have a favorable safety and tolerability profile and be appropriate considering comorbidities, age, gender, and urgency of action. When adjunctive therapy is chosen, it will be important to consider the potential for pharmacokinetic and pharmacodynamic interactions with the original anti-seizure medication. Pharmacokinetic interactions are most often related to enzyme induction or enzyme inhibition, while pharmacodynamic interactions are related to mechanism of action. It is preferable to avoid combining two seizure medications with the same mechanism of action. The combination of two anti-seizure medications with the same mechanism is more likely to be associated with adverse effects, even when the concentrations are within therapeutic range, and may also be less effective than a combination of two medications with different mechanisms. In particular, the combination of two sodium channel blockers such as carbamazepine and lamotrigine or lacosamide and carbamazepine has been associated with a higher incidence of dizziness, blurred vision, diplopia, and ataxia. Several studies have demonstrated that the combination of two medications with different mechanisms is more likely to be effective that combining two medications with the same mechanism. Some combinations may be synergistic, resulting in greater efficacy than expected. Such synergy has been best demonstrated with the combination of valproate and lamotrigine, but is suspected to occur with some other combinations as well.
Anti-seizure medications appropriate for initial monotherapy in adults (alphabetical order).

- **Carbamazepine.** Carbamazepine acts by blocking the sodium channel, reducing high-frequency neuronal firing. It is available as an oral preparation, but a parenteral preparation was recently marketed. Carbamazepine is a potent inducer of hepatic enzymes and also induces its own metabolism (autoinduction), so that its serum concentration decreases over the first 2-4 weeks of use. The half-life once autoinduction is complete is 12-17 hours. Carbamazepine's half-life increases in the presence of drugs that inhibit its metabolism, potentially resulting in accumulation and toxicity. The list of agents causing such accumulation includes erythromycin and other macrolide antibiotics (but not azithromycin), fluoxetine, propoxyphene, and grapefruit juice. The carbamazepine starting dose is 200 mg per day (100 mg twice a day when using the immediate release preparation or 200 mg at bedtime when using the extended-release preparation). The dose can be increased by 200 mg every 3 days, with a usual initial target dose of 400-600 mg per day in two divided doses. The extended-release preparation provides a steadier serum concentration and has been demonstrated to have superior efficacy. The dose can be titrated further as needed for seizure control. The suggested serum concentration is 4-12 mcg/ml.

- **Eslicarbazepine acetate.** Eslicarbazepine acetate is rapidly converted to the active metabolite (S)-licarbazepine, which is the active enantiomer of the monohydroxy derivative of oxcarbazepine. It has a similar mechanism of action to carbamazepine, blocking voltage-gated sodium channels and stabilizing the inactive state of the channel. The half-life of eslicarbazepine is 13-20 hours, but longer in the CSF. Eslicarbazepine is a weak inducer of CYP 3A4, responsible for estrogen metabolism and a weak inhibitor of CYP 2C19, involved in phenytoin metabolism. Eslicarbazepine can be dosed once daily, which is justified by its longer CSF half-life. The recommended starting dose is 400 mg once daily, to be increased to 800 mg once daily after 1 week. The dose can be increased again if needed to 1200 mg and even 1600 mg daily. Eslicarbazepine acetate should be avoided in idiopathic generalized epilepsy.

- **Ethosuximide.** Ethosuximide blocks T-type calcium currents, which predicts efficacy against absence seizures. It is a narrow-spectrum anti-seizure drug, effective only against generalized absence seizures. It has a long half-life of 30-60 hours. Despite the long half-life, it has to be administered in divided doses due to gastrointestinal adverse effects. Ethosuximide is the anti-seizure drug of choice for generalized absence seizures as the only seizure type. The starting dose is 250 mg twice daily (less for children younger than 6 years). The dose can be increased by 250 mg every week as needed for persistent seizures. The usual maximal dose is 500 mg three times a day. The recommended therapeutic range is 40 mg/L to 100 mg/L.
- **Gabapentin.** Gabapentin’s mechanism of action is binding to the alpha-2-delta subunit of voltage-gated calcium channels. Gabapentin is a narrow-spectrum agent against focal seizures. Its half-life is 5 to 7 hours, so it needs to be administered in three divided doses. Another reason for divided doses is low bioavailability and active transport system from the gut, which can be saturated. The recommended starting dose is 300-400 mg/d, to be increased by 300-400 mg every day up to 300 mg to 400 mg three times a day. The dose can be increased as needed up to 4800 mg/d in three divided doses.

- **Lacosamide.** Lacosamide blocks sodium channels, enhancing their inactive state. While the effect is similar to carbamazepine, it is slightly different in that lacosamide enhances slow inactivation, while carbamazepine and most other sodium channel blockers enhance fast inactivation. It has minimal pharmacokinetic interactions. Lacosamide has narrow-spectrum activity against focal seizures, but it does not appear to exacerbate absence or myoclonic seizures. The half-life is approximately 13 hours. The starting dose is 100 mg/d for 1 week (given once at bedtime or in two divided doses), then 100 mg twice a day. The dose can then be increased as needed by 100 mg every 1 to 2 weeks. The usual maximal dose is 600 mg/d in two divided doses.

- **Lamotrigine.** Lamotrigine also blocks sodium channels, like carbamazepine. However, it is likely to have unrecognized mechanisms to explain efficacy against absence seizures. It is a broad-spectrum anti-seizure drug. It is less sedating and has less negative impact on cognitive functions than many other anti-seizure medications. Its half-life is approximately 24 hours in monotherapy. However, its clearance is markedly affected by some concomitant medications and by pregnancy. Valproate more than doubles its half-life and estrogen (and pregnancy) reduces its half-life considerably. Lamotrigine requires a very slow titration to reduce the risk of rash. It should be started at 25 mg/d for 2 weeks, followed by 50 mg/d for 2 weeks, then 100 mg/d. This may be a sufficient dose in the elderly, but the usual initial target dose is 100 mg twice daily. The dose can be increased as needed by 100 mg every 2 weeks. The suggested therapeutic range is 2-20 mcg/ml. Once daily dosing is possible with the extended-release preparation.

- **Levetiracetam.** Levetiracetam acts by binding to the synaptic vesicle protein SV2A, which seems to result in decreased neurotransmitter release under hyper-excitatory conditions. It appears to have a broad spectrum of efficacy. It has no significant pharmacokinetic interactions. Its half-life is 6 to 8 hours. The immediate release preparation has to be given twice a day, but a once daily extended-release preparation is available. While a starting dose of 1000 mg per day is acceptable, it is best to start with a lower dose of 500 mg/d. The dose can then be increased as needed and as tolerated up to 3000-4000 mg/d.
• Oxcarbazepine. Oxcarbazepine is a structural analogue of carbamazepine, but with major differences in metabolism and interactions. It is a pro-drug, rapidly converted to the active metabolite responsible for its anti-seizure activity, a monohydroxy derivative. It is a weak inducer of CYP 3A4, which metabolizes estrogen, and a weak inhibitor of CYP 2C19, which metabolizes phenytoin. It does not induce its own metabolism. It is a sodium channel blocker like carbamazepine. It is a narrow spectrum agent which may aggravate generalized absence and myoclonic seizures. The half-life of the active metabolite is 8 to 10 hours. Oxcarbazepine has to be given twice daily, but an extended release preparation allows once daily dosing. It can be started at 600 mg per day, but unless rapid action is urgently needed, it may be wise to start with 300 mg per day for the first week. The dose can be titrated by 300 mg per week as needed. The usual maximal dose is 2400 mg per day. The recommended therapeutic range for the monohydroxy derivative is 15-35 mcg/ml.

• Phenobarbital. Phenobarbital’s main mechanism of action is on the GABA-A receptor, prolonging the opening of the chloride channel associated with that receptor. Phenobarbital induces liver enzymes, reducing the concentration of agents metabolized by these enzymes. Phenobarbital is effective against focal and generalized tonic-clonic seizures, but not generalized absence seizures. Because of its sedative and adverse cognitive effects, it is rarely a first-line treatment in developed countries, but it is the only affordable anti-seizure medication in many developing countries. Its half-life is 80-100 hours, justifying once daily dosing. The starting dose of 30-60 mg at bedtime. The dose can be increased by 30 mg to 60 mg every 2 weeks as needed, depending on seizure control and tolerability. The recommended serum concentration is 15-40 mcg/ml.

• Phenytoin. Phenytoin blocks the sodium channel, prolonging its fast inactivated state. It is a narrow spectrum agent, which may exacerbate myoclonic and absence seizures. It is a potent hepatic enzyme inducer, reducing the efficacy of agents metabolized by the liver. Phenytoin half-life has a wide range, with an average of about 22 hours. Its half-life increases with increasing dose due to nonlinear pharmacokinetics resulting from saturable metabolism. The usual phenytoin initiation dose is 200-400 mg/d, initially given as a bedtime dose. It can be titrated based on clinical response, but serum concentration should be considered. The phenytoin plasma level may increase disproportionately with an increase in the dose, so small increments such as 30 mg to 60 mg should be used when in the therapeutic range. The recommended “therapeutic” serum concentration is 10-20 mcg/ml. Phenytoin is usually 90% protein-bound, and the recommended protein-free concentration is 1-2 mcg/ml. The protein-free concentration should be checked whenever a change in protein binding is suspected (such as in hepatic or renal failure, in low protein states, in the elderly, or in the presence of other agents such as valproate competing for protein binding).
• **Topiramate.** Topiramate has multiple mechanisms of action, including antagonism of AMPA/kainate receptors, augmentation of GABA activity, and blocking of voltage-gated sodium channels. It has minimal interactions- it is a mild inducer of CYP 3A4, which metabolizes estrogen, and a mild inhibitor of CYP 2C19 which metabolizes phenytoin. It is a broad-spectrum anti-seizure medication, but not usually effective against absence seizures. Topiramate’s half-life is approximately 21 hours. It is indicated for twice daily administration, but once daily administration can be considered. Extended release preparations are available and are indicated for once daily administration. Topiramate has to be titrated gradually to alleviate cognitive adverse effects, and there is a suggestion that the extended release preparations have less cognitive adverse effects. While a starting dose of 50 mg daily is approved, it is better to start at 25 mg/d and increase the dose by 25 mg every week up to 100 mg/d. The dose can be increased as needed by 25-50 mg every week. The usual maximal dose is 400 mg/d.

• **Valproate.** Valproate has multiple mechanisms of action including GABA potentiation, blocking of T-type calcium channels (predictive of efficacy against absence seizures), and blocking of sodium channels. Valproate has a broad spectrum of efficacy against all seizure types. It remains the most effective drug for idiopathic generalized epilepsy with generalized tonic-clonic seizures. Valproate is a potent hepatic enzyme inhibitor, reducing the clearance of several medications. It is extensively metabolized by the liver. Its half-life is 13-16 hours, requiring divided doses unless the extended release divalproex sodium preparation is used. Valproate should be started at a low dose to improve tolerability, preferably using the extended-release preparation. The recommended starting dose is 500 mg per day. The dose can be increased gradually as needed to achieve seizure control, up to 1000-2000 mg/d. The recommended therapeutic concentration range is 50-100 mg/L. Valproate is 90% protein-bound. The free fraction increases with increasing total concentration. A protein-free concentration should be checked at high levels and other situations where a protein binding may be altered such as with low protein states and with phenytoin coadministration (due to competition for protein binding).

• **Zonisamide.** Zonisamide has multiple mechanisms of action, including blocking T-type calcium channels (predictive of efficacy against absence seizures), blocking sodium channels, and weak inhibition of carbonic anhydrase activity. It is a broad spectrum anti-seizure drug, though only indicated for focal seizures. It is metabolized in the liver but has minimal interactions. It has a long half-life of about 60 hours, justifying once daily dosing, even though the official indication calls for divided doses. The starting dose is 100 mg at bedtime for 2 weeks, then 200 mg at bedtime. The dose can be increased by 100 mg every 2 weeks as needed, up to 600 mg/d. The suggested therapeutic plasma concentration is 10-40 mcg/ml.
Table 1. Spectrum of efficacy of AEDs in various seizure types and FDA indications for specific syndrome and non-seizure indications

<table>
<thead>
<tr>
<th>ANTI-SEIZURE DRUG</th>
<th>FOCAL SEIZURES</th>
<th>GENERALIZED TONIC-CLONIC SEIZURES</th>
<th>GENERALIZED ABSENCE SEIZURES</th>
<th>GENERALIZED MYOCLONIC SEIZURES</th>
<th>LENNOX-GASTAUT SYNDROME (LGS) OR INFANTILE SPASMS (IS) FDA INDICATION</th>
<th>NON-SEIZURE FDA INDICATIONS</th>
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<td>Unknown</td>
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<td>ANTI-SEIZURE DRUG</td>
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<td>Not efficacious</td>
<td>Not efficacious</td>
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<td>LGS</td>
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<td>Efficacious #</td>
<td>Probably efficacious #</td>
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</table>

Efficacious: efficacy proven in Class I-II trials

Probably efficacious: Efficacy suggested, but not proven in Class I-II trials

# Appropriate for initial monotherapy based on clinical trial data and AAN-AES guidelines
REFERENCES


