



# Tuberous Sclerosis Association

## Anti-epileptic drugs: how they treat seizures and their unwanted side-effects

### Introduction

Approximately 65-75% of people with tuberous sclerosis (TS) will have epilepsy. Most epilepsy starts in children and there are many different types of epilepsy (see: 'Tuberous sclerosis and epilepsy'). The vast majority of people who have epilepsy will take anti-epileptic drugs (AEDs) - also called anticonvulsants - to try and control the seizures. The epilepsy that occurs in people with TS is often difficult to control. This is particularly true if the epilepsy starts in early childhood or the person had moderate or severe learning difficulties.

It may take a while to find the right medicine or amount (dose) of a medicine that works best for the person, whether a child or adult. Sometimes children and even some adults will need to take a combination of two AEDs - and this is called polytherapy. It is very rare for anyone to need treatment with more than two AEDs at the same time. There is no good scientific evidence that three AEDs will control seizures better than two. Also, people taking three AEDs are far more likely to have unwanted side-effects from the combinations of the different medications.

### Which anti-epileptic drug (AED)

The choice of AED depends on the type of seizure or the type of epilepsy (the epilepsy syndrome) the person has. The simple guide

below shows the most commonly used AEDs for treating these different seizures or syndromes:

The specialist doctors (called paediatric or adult neurologists) who treat people with TS and epilepsy will prescribe the AED that is best for the type of epilepsy syndrome or type of seizure(s) that your child has. The specialist will also take into account the possible unwanted side-effects of these medications as well as how the medications come. Anti-epileptic drugs may come as tablets, capsules, flavoured liquids or powders that can be dissolved in water or juice. The specialist epilepsy doctor or nurse will explain how to give the medicine(s).

It is important that people always receive the same brand of the antiepileptic medicine because different brands are not always the same. It is important for parents and patients to keep a note of which brand(s) they take and to show this to the local chemist or pharmacy when collecting the next supply so that they receive the same brand.

Some medicines that you may get on prescription or buy from a pharmacy do not work properly if taken with anti-epileptic drugs. Also, some medicines for epilepsy work less well if taken with other drugs. It is therefore important to check with a pharmacist or doctor before giving other medicines to your child. Some

Seizure type (epilepsy syndrome)	First choice AED	Other AEDs that are used
Infantile spasms (West syndrome)	Vigabatrin	Corticosteroids Nitrazepam Sodium valproate
Focal (partial seizures)	Carbamazepine	Lamotrigine Levetiracetam Clobazam Topiramate
Generalised tonic-clonic	Sodium valproate	Carbamazepine Lamotrigine Levetiracetam Topiramate
Myoclonic	Sodium valproate	Levetiracetam Clobazam / clonazepam Topiramate
Atonic or tonic	Sodium valproate	Lamotrigine Levetiracetam Rufinamide Clobazam
Lennox-Gastaut syndrome	Sodium valproate	Rufinamide Lamotrigine Levetiracetam

medications such as the oral contraceptive pill may also interact with some of the AEDs. This could mean that the oral contraceptive may not be as effective. The AEDs that are known to reduce the effect of the oral contraceptive pill include:

- carbamazepine
- oxcarbazepine
- phenytoin
- phenobarbital
- topiramate

Many medicines used to treat epilepsy have some unwanted side-effects for the first few days or weeks. To keep this to a minimum the person will usually start by taking a small amount (dose) of the AED and then the dose will be gradually increased. The medication may be taken once a day to begin with but after a week or so it is usually given twice a day. This means that the person may continue to have some seizures for a week or two until the AED is at the right dose. Some AEDs have to be started and increased very slowly and this is particularly the case for lamotrigine and carbamazepine.

Fortunately most unwanted side-effects are mild and do not last long. The most common ones include sleepiness or drowsiness and occasionally nausea or vomiting (feeling or being sick). Rarely, some people may also complain of feeling rather bad-tempered. These side-effects usually wear off after a week or two.

More serious side-effects include a rash and this is particularly likely with the AEDs lamotrigine (the brand name of which is Lamictal), carbamazepine (the brand name is Tegretol), oxcarbazepine (the brand name is Trileptal) and phenytoin (the brand name is Epanutin - but this AED is used only very rarely now). It is important to understand that this rash will only occur in 5 to 8 out of every 100 people who take these AEDs. It is also important to stop taking the AED and to seek urgent medical advice if a rash does occur within the first few weeks of taking one of these medications.

The following outlines the most commonly-used anti-epileptic drugs and their most common side-effects

*Carbamazepine (Tegretol and Tegretol Retard)*: the main unwanted side-effects are caused by starting the drug in too high a dose and can be prevented if it is started slowly and increased over at least 3 to 4 weeks. The most common is a rash which affects the whole body but goes away once the drug is discontinued. Other quite common unwanted side-effects include drowsiness, feeling sick (nausea), seeing double (diplopia), poor co-ordination and headaches. A very rare side-effect is a lowered immunity to fight infection because the medication can lower the white cells in the blood which fight infections.

*Clobazam (Frisium) and clonazepam (Rivotril)*: these belong to a group of AEDs called the 'benzodiazepines'. Diazepam, lorazepam, midazolam and nitrazepam are also benzodiazepines (these AEDs are described a bit later). The benzodiazepines can be very effective AEDs in treating different types of seizures including myoclonic, atonic, focal (partial) and tonic-clonic seizures. Clobazam is used more frequently than clonazepam because it is better at controlling focal and tonic-clonic seizures. The main

side-effects of clobazam and clonazepam include sleepiness and unsteadiness which usually wear off after a couple of weeks. Clonazepam can also cause excessive drooling, excitement and hyperactivity, particularly in children. Because of this clonazepam is used only rarely in children with TS. One of the main side-effects of clobazam and clonazepam is something called 'tolerance'. This means that over many weeks, sometimes months, these AEDs do not work as well. When the dose is increased seizure control might improve a little but the person is more likely to become very sleepy. If this happens, the clobazam or clonazepam will usually be slowly discontinued.

*Corticosteroids (prednisolone, ACTH, tetracosactide, hydrocortisone)*: these are not proper anti-epileptic drugs. Doctors are not sure why these medications work in some types of seizure - but they can do! They are used in only two situations. The most common reason for using a corticosteroid is to treat infants and young children with infantile spasms (West syndrome). The other situation is in the rare type of epilepsy called 'non-convulsive status epilepticus'. Prednisolone and hydrocortisone are given by mouth. ACTH and tetracosactide are given by intramuscular injection which can be painful for the infant. Corticosteroids are usually given for a very short time and usually for no more than 4 or 6 weeks, sometimes less. This is because of side-effects associated with these medications some of which can be very serious. These include the following: irritability, hyperactivity, increased appetite and weight gain, disturbed sleep, high blood pressure and a lowered resistance to fight severe infections (called 'immunosuppression').

*Diazepam (Diazemuls; Diazepam Rectubes, Stesolid)*: this is another type of benzodiazepine (like clobazam). Its only use in the treatment of epilepsy is an emergency situation. It is used to try and stop a tonic-clonic seizure that has been lasting for more than 5 minutes or to stop repeated seizures that have been happening for 30 minutes. It can be given out of hospital and also in hospital. It comes in a tube (called a Diazepam Rectube or Stesolid) and is squirted up the back passage (the rectum). In hospital it can be given this way but it can also be given by intravenous injection. Diazepam causes sleepiness and most people will fall asleep after they have been given it. Midazolam has largely replaced diazepam to try and stop seizures out of hospital (midazolam is described a bit later).

*Ethosuximide (Zarontin; Emeside)*: this medication is used only to treat absence seizures and this seizure type is very unlikely to occur in TS. It has no effect on focal or tonic-clonic seizures and is only really prescribed to children. The main side-effects are nausea and diarrhoea and also a constant, but mild headache. These side-effects go away when the medication is slowly discontinued.

*Gabapentin (Neurontin)*: this is not felt to be a particularly powerful AED, but it can be effective in treating focal (partial) seizures. It does have very few side-effects and the main ones are behavioural changes (which occur in about 10 in every 100 people treated with this medication) and occasionally some abnormal movements. The other main problem with this medication is that it often has to be taken three times a day. Nearly all the other AEDs can be taken twice, or sometimes, just once a day.

*Lacosamide (Vimpat)*: this one of the newer AEDs and is effective in treating focal (partial) and generalised tonic-clonic seizures. There is not enough information about whether it might be effective in the treatment of other types of seizure. The main side-effects of lacosamide are dizziness and nausea (feeling or being sick) which are more likely to occur if the person is also taking carbamazepine or oxcarbazepine at the same time. The dizziness is thought to affect between 10 and 15 in every 100 people who take this AED.

*Lamotrigine (Lamictal)*: this has very few unwanted side-effects. The main one is a rash which usually occurs within the first three weeks after starting the drug. This could be serious and if it does occur, no more of the drug should be given until the person has been seen urgently by their GP or in the local Accident and Emergency Department. If used in high doses it may cause headaches and difficulty sleeping. The effect of lamotrigine is reduced if the person is pregnant or is taking the oral contraceptive. Lamotrigine may also interact with carbamazepine and sodium valproate, two of the most common AEDs that are often used to treat epilepsy.

*Levetiracetam (Keppra)*: this is quite a new AED and seems to have very few unwanted side-effects. As with most AEDs, people may complain of some sleepiness when it is first started but this wears off. The other main side-effect is behaviour change causing irritability and bad-temperedness. However, this only occurs in 8 or 10 out of every 100 who take this medication.

*Lorazepam (Ativan)*: this is another type of benzodiazepine (like clobazam). It is only used in epilepsy to treat a tonic-clonic seizure that has lasted longer than 5 minutes and in hospital. It is given by intravenous injection. In the future lorazepam may become available as a very thin tablet or 'wafer' that is put under the tongue and that melts rapidly to stop a tonic-clonic seizure at home. Its main side-effect is sleepiness and many people will fall asleep after it has been given.

*Midazolam (Epistatus; Hypnovel)*: this is another type of benzodiazepine (like clobazam, diazepam and lorazepam). Its only use in the treatment of epilepsy is to try and stop a tonic-clonic seizure that has been lasting for more than 5 minutes or to stop repeated seizures that have been happening for 30 minutes. It can be given out of hospital and in hospital. It is given into the cheek cavity (called the buccal cavity) - which is the space inside the cheek. It is not put into the mouth. The main side-effect is sleepiness and most people will fall asleep after it has been given.

*Nitrazepam (Mogadon)*: this is another type of benzodiazepine (like clobazam, lorazepam and midazolam). It is only really used to treat the seizure type, infantile spasms. In infants less than 12 months of age infantile spasms is the type of seizure that occurs in West syndrome. The medication can also be used sometimes to treat epileptic spasms that occur in older children. The main side-effects of this AED are sleepiness and excessive drooling. Most children who receive this medication do so for 6 to 12 months.

*Oxcarbazepine (Trileptal)*: this is very similar to carbamazepine (Tegretol) that has been described earlier. Oxcarbazepine is considered to have similar but less frequent fewer side-effects than carbamazepine. However, oxcarbazepine does not come as in a

slow-release tablet and so it will always have to be given twice, or rarely, three times a day.

*Phenobarbital (Phenobarbital)*: this is the oldest AED and although it may be effective in treating tonic-clonic, atonic and myoclonic seizures it is rarely used today. It is only really used as an anti-epileptic drug of last choice - when the other AEDs have not worked. The main side-effects are an allergic rash, sleepiness, hyperactivity and mental slowing (which can be a big problem for school children), and weak bones (called 'osteoporosis' or 'osteopaenia'). The medication reduces the effect of the oral contraceptive pill and may cause malformations of the developing baby during pregnancy.

*Phenytoin (Epanutin)*: this is one of the oldest AEDs and although it is quite a powerful medication it is used only very rarely in Great Britain - and hardly ever in children with TS. The medication is associated with many unwanted side-effects. These include an allergic rash, unsteadiness, abnormal movements, nausea (feeling sick) and double vision. When used for many months or years it can also cause thickening of the gums and unhealthy teeth, roughening of the skin of the face and vitamin D deficiency which leads to weak bones (called 'osteoporosis' or 'osteopaenia'). Phenytoin also affects the developing baby during pregnancy and cause malformations such as spina bifida, cleft lip and palate and heart defects. Phenytoin also reduces the effect of the oral contraceptive pill. Finally, people who take phenytoin will usually need to have blood tests to measure the level of the medication in the blood.

*Pregabalin (Lyrica)*: this AED is very similar to gabapentin. An additional unwanted side-effect is an increased appetite.

*Rufinamide (Inovelon)*: this is a very new AED and is mainly used in children with the type of epilepsy called the Lennox-Gastaut syndrome. It is effective in stopping the 'drop attacks' in this epilepsy that are caused by atonic and tonic seizures. However, rufinamide might also be effective in treating focal (partial) seizures. The main side-effects are vomiting and diarrhoea and also sleepiness and behaviour changes. More information is still needed on this AED because it has only been used in Great Britain for the past few years.

*Sodium valproate (Epilim; Epilim Chrono; Episenta)*: this is one of the most effective and also the most commonly used AED in Europe. When used alone it causes very few unwanted side-effects. The main side effects are some sleepiness or irritability (mainly in children) as the medication is first started. It can frequently increase a person's appetite leading to an increase in weight. This is more commonly seen in girls and young women rather than in boys. The medication can also cause some hair loss in the first six months after it has been started. The hair always grows back and when it does it is usually thinner and curlier. High doses of the medication may also cause a tremor (shakiness). There is a very rare side-effect of liver damage in young children aged less than 3 years who have a biochemical (metabolic) cause for their epilepsy. This risk of liver damage does not seem to be a problem in young children with TS. The main unwanted side-effects are in older girls and young women. It may cause problems with the menstrual cycle (periods) and might affect the developing baby during pregnancy resulting in malformations. This is more

likely if sodium valproate is taken at the same time as other AEDs. These are very important side-effects. Because of this, the use of valproate must be carefully considered and discussed with females of child-bearing age and potential.

*Sulthiame (Ospolot)*: this is an old AED that is used a lot in Germany, Austria and other European countries. It is only rarely used in Great Britain. It is useful in treating focal (partial) seizures and some people with tonic-clonic and myoclonic seizures. There are only a few unwanted side-effects such as sedation and rarer side-effects including hyperpnoea (breathing more rapidly) and some mental slowing.

*Topiramate (Topamax)*: this can be an effective medication in stopping seizures. Unfortunately, it may cause a number of unwanted side-effects. The main ones are a reduction in appetite which, in children can lead to some weight loss which might affect their growth. The other side-effects include mental slowing which means that people may not be able to think or talk as well. This can affect up to 20 in every 100 people who take the medication. The other side-effect is on behaviour making some people angry or very sad and this happens in 5 or 10 out of every 100 people on this AED. All of these side-effects will go away when the medication is slowly withdrawn. The last and least common side-effects are kidney stones and pressure in the eye (called 'glaucoma').

*Vigabatrin (Sabril)*: this medication is mainly used in treating children who have infantile spasms (West syndrome). Vigabatrin is actually the medication of first choice in treating children with infantile spasms caused by TS. The main unwanted side-effects in treating infantile spasms are sleepiness and irritability - but these usually wear off after a few days. Rarely, the medication may also increase the child's appetite. It may also worsen some other seizure types - particularly myoclonic seizures. Vigabatrin also used to be prescribed for focal (partial) seizures but because of one particular side-effect it is far less commonly used. This side-effect is reduced peripheral vision so that a person may have difficulty seeing things at the edge of their vision. It is recommended that if a person is to take vigabatrin then their peripheral vision (visual fields) should be examined before starting the drug and every 4 to 6 months whilst they remain on it. Children who have learning difficulties are not usually able to have this test because it requires concentration and co-operation.

*Zonisamide (Zonegran)*: this is quite a new AED to be used in Great Britain. It seems to be effective in a wide range of different types of seizure. It is quite similar to topiramate which has been described earlier. However, zonisamide has fewer unwanted side-effects and particularly causes less mental slowing and behaviour changes than topiramate. Zonisamide may also cause kidney stones.

*Other, less commonly used anti-epileptic drugs:*

There are a number of other AEDs that may be used in treating people with epilepsy and TS. They are only prescribed in certain situations. These are:

*Acetazolamide (Diamox)*: this is a very weak AED and is only used in conjunction with either carbamazepine or oxcarbazepine. Side-effects are uncommon and include nausea, reduced appetite and occasionally, tingling in the fingers and toes.

*Paraldehyde*: this is a very old anticonvulsant that is now only used very rarely and mainly in children. It is only ever used to try and stop a tonic-clonic seizure that has been lasting for more than 5 minutes or to stop repeated seizures that have been happening for 30 minutes. It comes as a ready-made mixture with olive oil and is squirted up the back passage (rectum). It has a very powerful smell and causes children to sleep after it has been given. It is far less commonly used instead of a benzodiazepine (midazolam or diazepam) as the child's emergency (also called 'rescue') medication. It can also be used in hospital.

*Stiripentol (Diacomit)*: this medication is mostly used for a quite rare epilepsy syndrome called Dravet syndrome (also known as 'severe myoclonic epilepsy of infancy'). However, it may occasionally be used to treat myoclonic and tonic-clonic seizures in different epilepsy syndromes. It does have a few unwanted side-effects including sleepiness during the day but insomnia (difficulty falling asleep) at night. It can also cause a loss of appetite and some behaviour problems. As will all the AEDs, these side-effects go when stiripentol is gradually discontinued.

*Tiagabine (Gabitril)*: the main side-effect is dizziness and nausea. Rarely it may make some seizures worse - particularly myoclonic and absence seizures.

*New anti-epileptic drugs*

There are also some brand new AEDs that have recently become available and there is not much information on these medications. These include:

*Eslicarbazepine (Zebinix)*: probably similar to carbamazepine and oxcarbazepine in how it acts and its side-effects. This AED may only need to be given once a day.

*Retigabine (Trobal)*: no information on this AED

Information about the practical aspects of giving anti-epileptic drugs to children and all the likely side-effects that may occur with the different AEDs can be found at the following website: [www.medicinesforchildren.org.uk](http://www.medicinesforchildren.org.uk)

Much more detailed, but sometimes difficult to read information, can be found with the information leaflet that comes with the medicine.

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Further information on TSC and the work of the Tuberous Sclerosis Association can be obtained from our website at: [www.tuberous-sclerosis.org](http://www.tuberous-sclerosis.org)

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