# Adverse Effects of Antiepileptic Drugs (AEDs)

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There are so far at least 25 AED available, each with a different profile. It is almost impossible for the practicing neurologist or epileptologist to have a thorough understanding of each drug. The risk is that the treating neurologist will only use the drugs that he is acquainted with, not daring to combine it with those not entirely known but maybe more effective. In this handout AEDs refer actually to antiseizure drugs, but the term AED is the most common term used.

Thus it is important to try to develop a systematic pathway to facilitate the understanding of AES adverse effects (AE). The best review of this subject can be found in the paper "Perucca P(1), Gilliam FG., Adverse effects of antiepileptic drugs. Lancet Neurol. 2012 9:792-802. This is a good review which is easy to refer to when needed and the most comprehensive so far.

Adverse events or side effects (AEs) are usually divided into 5 major categories according to World Health Organization. The different types are:
Type A effects: Attributed to the known mechanism of action
Type B effects: Idiosyncratic effects that cannot be explained based on the know MOA of a drug and are unpredictable.
Type C effects: Chronic drug reactions due to chronic exposure such as weight gain
Type D effects: Teratogenic or carcinogenic AEs
Type E effects: Interactions of the AES with other drugs.

Below are the most common AEDs and their abbreviations that will be used in this text
Abbreviations of AEDs:
CBZ- carbamazepine
CLB- Clobazam
CLN - Clonazepam
ESL- Eslicarbazepine acetate
ETH- Ethosuximide
FEL-Felbamate
GBP- Gabapentin
LCM- Lacosamide
LTG- Lamotrigine
OXC- Oxcarbazepine
PB-Phenobarbital
PER- Perampanel

PHT- Phenytoin
PRI-Primidone
PRE-Pregabalin
RUF- Rufinamide
STI- Stiripentol
TPM. Topiramate
VPA- Valproic acid
VGB-Vigabatrin
ZON-Zonisamide

**I.Type A Effects**

A. Titration Adverse Effects

Titration SEs can occur when AES are introduced too quickly. Sometimes it is important to obtain a therapeutic dose of the new drug as quickly as possible, and then the titration side effects cannot be helped and need to be accepted. However, in most cases introduction of an AED can be done in a calm and slow fashion which will result in the patient experiencing less SEs and discomfort.
The main method to prevent titration side effects is slow titration primarily by starting with low doses, often lower than that which is recommended by the package insert: The motto to remember is "**Start Low and Go Slow".**
The most common titration side effects are somnolence, CNS related side effects as dizziness, ataxia, nausea, cognitive problems, and allergic reactions. Most of these AEs are preventable by starting slowly. The main observation and lesson that most of us learn with time and experience is that tolerability to most AEDs are almost always improved by slow titration.

B. Seizure Aggravation

Seizure aggravation is a problem that is encountered when the drug given is inappropriate for the seizure type or when a drug elicits a completely new seizure type in the patient. Aggravation means an increase in seizure frequency by 100%. Many examples of seizure aggravation are published. The drugs which are most associated with potential seizure aggravation when given to patients with generalized genetic related epilepsies are the fast-acting sodium channel blocking agents like CBZ, LTG, PHT and OXC. VGB has also been implicated in seizure aggravation for similar seizure types, especially absence epilepsy. Fast-acting sodium channel blocking agents can often exacerbate myoclonic jerks especially in patients with JME

If a patient, after receiving a new AED, develops a new seizure type, then the first thing to consider is that the new drug may be inappropriate for that person or his seizure syndrome. Reevaluate if the drug should be stopped. If the seizure type disappears after stopping the drug, then it is probably due to the AED. Re-challenge is an option, but often the patient is not willing to test the drug again.

C. Other Type A effects are those attributed to the known mechanism of action (MOA):

1. Voltage-gated sodium (Na+) channels (VGSC)

Many AEDs have VGSC MOAs. The most common is the fast-acting blocking mechanism as seen in CBZ, PHT, OXC, LTG. These drugs are very effective in focal onset seizures but may exacerbate other seizure types such as myoclonic jerks. Other newer AEDs such as LCM, ESL and RUF seem to primarily affect the slow-acting mechanism of the VGSC, thus appearing to have a somewhat broader spectrum of action. Still for all these compounds, the VGSC typical side effects are CNS related such as ataxia, dizziness, nausea and vomiting when given in high doses, nystagmus, diplopia, and with high doses, tremor.

Prolonged Q-T time is a know side effect of VGSC drugs. This is usually not a significant AE, but the physician need to be aware of the risk of giving VGSC drugs to people who have AV-blocks and do not have a pacemaker. If deemed necessary, then ECG follow-ups are warranted.
Historically, VGSC drugs are not heavily implicated concerning psychiatric AEs as often as other drugs with other mechanisms of action. A combination of 2 VGSC drugs may give rise to pharmacodynamics enhanced CNS side effects, especially dizziness.

2. GABA

GABAergic drugs include the benzodiazepines (like CLB , CLN, PB) through their action on the GABA- a receptor as well as VGB which increases GABA through irreversible inhibition of GABA-transaminase. While GABAergic AED action on the alpha-receptor seems to have a broad spectrum of effect, VGB actually increases whole brain GABA and can exacerbates seizure types such as absence and myoclonic jerks. On the other hand VGB is effective in infantile spasms and focal onset seizures. The main non-idiosyncratic adverse effects of VGB are drowsiness and also in some cases depression and agitation, especially in children.

2. AMPA

Post-synaptic AMPA receptor inhibition is a mechanism found only in PER and to a lesser extent in TPM. The main AEs for this MOA is dizziness and irritability. In people with behavioral disorders who are aggressive, these AEDs should be used with caution.

4.Voltage-gated calcium channels

This MOA is found in ETH, GBP, and PRE. Drugs with multiple mechanisms of action like ZON, LEV, TPM and VPA also have calcium channel modulating characteristics. Often these drugs have relatively less side effects than other types and usually do not cause major psychiatric and behavioral disturbances.

5. Synaptic vesicle protein 2a

SV2a vesicle inhibition is a rather new MOA and found in LEV and BRI, both produced specifically for these attributes. However, both have other MOA as well although the SV2a inhibition is thought to be the major MOA for epilepsy. LEV and to a lesser degree BRI can cause depression and aggression in about 10-20% of patients. It is important to follow patients on LEV and evaluate their mental condition at each visit, especially during the first few months. Drowsiness is a common complaint but can be addressed by slow titration and even the use of caffeine. LEV inhibits calcium release from the endoplasmic reticulum by inhibiting ryanodine receptors while caffeine has the opposite effect.

6. Multiple MOA
TPM, VPA and ZON have multiple mechanisms of action and all have varied side effects. TPM and ZON cause weight reduction while VPA causes weight increase in a majority of patients. VPA causes tremor and hair loss and polycystic ovary syndrome. The most disturbing of VPA' s AEs is the increased risk of teratogenic malformations and lower IQ in offspring of women taking VPA. An FDA recommendation is that all women on VPA need to take folic acid BEFORE pregnancy, although the American Epilepsy Society feels this should apply to all women of child bearing age on AEDs.
TPM has major concerns at higher doses (especially >100 mg/day) causing word-finding disorders and slow thinking.
There have been increasing observations that VPA might cause dementia and Parkinson like symptoms. When stopped these symptoms quickly disappear.

In other words, certain side effects are found in almost every AED no matter which MOA is involved. These include drowsiness, dizziness, irritability, increased risk of suicidality and depression. The FDA has warned about the depressive effects of AEDs in some individuals. The recommendation is that all patients with epilepsy on AEDs need to be screened and followed -up for depressive symptoms.

**II. Type B Effects: effects that cannot be explained based on the known MOA of a drug and are unpredictable**.
Idiosyncratic AEs may still be dose dependent but are usually unpredictable. The AEs seen can involve any organ but mainly the skin as in allergic reactions. The most common types of ISAEs are Agranulocytosis, aplastic anemia, skin rash, hepatic necrosis, allergic dermatitis, and pancreatitis.

Certain ethnic groups are more susceptible to allergic reactions. For CBZ and OXC, people with a mutation of HLA are more susceptible. Studies have shown that many Asian ethnic groups as Han Chinese have the mutation HLA B*1502 which increases the risk for Steven-Johnson skin rash. The FDA has warned against using CBZ and OXC in patients of Asian descent without first testing for HLA-B*1502.
The most important acute idiosyncratic reactions are:
1. Allergic dermatitis as Steven Johnson Syndrome: Drugs most know to elicit such reactions are CBZ, ETH, FBM, GBP, LTG, PB, PHT, TPM, OXC, VPA and ZNS.

2. Antiepileptic Hypersensitivity Syndrome which is unusual but important to recognize because of its life threatening condition: CBZ, ETH, LTG, PB, PHT and VPA.
3. Pancreatitis and Hepatic failure: seen mainly in CBZ and VPA

There are also elusive Idiosyncratic AEs that take many years before they are recognized. The most important are the discovery of the Shoulder-Hand syndrome for phenobarbital which took 22 years before detected (1912-1934), aplastic anemia for felbamate which took a year before recognized, VPA hepatotoxicity which took 10 years (1967-1977) and VGB with the occurrence of irreversible peripheral visual side effects with a latency of 8 years between 1989 to 1997 (probably now in the category of chronic SEs).
To minimize the risks for idiosyncratic AEs it is important to inform patients about the potential risks and which symptoms to look for and to have a screening program for high-risk patients. Doing HLA mutation analyses is one method as well as following patients on VGB with repeated visual field evaluations.

**III. Type C AEs: Chronic Effects**
Chronic side effects are seen with cumulative dose and are often insidious because of the slow progression. Sometimes the patient does not even notice. The most common are below with the drugs most likely implicated.
Hyponatremia – Seen mainly in CBZ related drugs: CBZ, ESL and OXC
Osteoporosis- Seen mainly in AEDs that have hepatic metabolism: CBZ, PHT, PB, VPA
Polyneuropathy- PHT
Cerebellar atrophy- PHT
Gingival hyperplasia-PHT
Behavioral disorders-aggression, irritation, depression, suicidality- Potentially all AEDs but most implicated are LEV, PER, TPM
Skin disorders-ache, psoriasis, and eczema- All implicated but mainly CBZ, PHT, LTG, ZON, PB
Hyperthyroidism: CBZ
Dyslipidemia- Most implicated is CBZ

Weight changes- Weight gain: VPA, VGB, PER, GBP and PRE
Weight loss: TPM, FEB, RUF, STI, ZON
Memory difficulties- all drugs implicated but especially TPM

**IV. Type D Reproduction Effects**
All AEDs can cause sexual dysfunction, although the mechanism for some AEDs is not known. For drugs that are metabolized in the liver, influence on the production of sexual hormonal is important. For example, for drugs metabolized by cytochrome p450 system, low dose contraceptive pills do not give adequate protection and high dose estrogen containing contraceptives need to be used. The drugs that are not implicated are: GBP, PRE, LCM, LEV, LCM, RUF, VGB, VPA,TPM (under 200mg/day), and ZON.

While LGT does not change the effectiveness of the contraceptive pill, the cyclic nature of the treatment with one week without the pill can cause fluctuations in the LTG levels resulting in seizures.

Valproate is in a separate class concerning reproductive health. Treatment with VPA causes weight gain and increased risk of polycystic ovary syndrome in young women. The risk is highest of all AEDs for teratogenic malformations as well as the decrease in IQ and the increase in behavioral disorders in offspring. For a more detailed list of the reproductive AEs that can occur, please see the section on the specific subject

**V. Type E Effects: Drug-drug Interactions**

Many of the older AEDs and some newer ones have drug-drug interactions. This usually arises because many of the AEDs are metabolized in the liver through the cytochrome p450 enzyme system. PHT, CBZ , PRI and PB are the ones that cause enzyme induction and are metabolized through systems like CYP2c9 and CYP2c19 or CYP3a4 which also affect many other drugs and hormones. The AEDs not metabolized by the liver which can be used especially in patients with concomitant medications and co-morbidities are: BRI, LEV, LCM, VGB, GBP, PGB,
Drugs with some drug interactions but less that the older drugs are: TPM, ESL, OXC, LTM.
VPA and LTG are metabolized through the *N*-glucuronidation system and VPA also inhibits liver enzymes causing the drug-drug interactions. Especially with LTG, VPA can strongly inhibit the metabolism of LTG complicating treatment. CYP2c9 and CYP2a6 inhibition are the predominant enzymes in the CYP-mediated oxidation of VPA. More than 600 drugs have interactions with VPA.

The rationale way to deal with suspected drug interactions is to monitor serum levels of each of the drugs that are added as well as those already being taken. Drug interactions can be very problematic when adding an AED that induces or inhibits liver enzymes when a patient is on anticoagulants, simvastatin and simvastatin- like compounds, contraceptives, chemotherapy, Immunotherapy , psychopharmacological agents, antibiotics,… and the list continues.

Thus, reasons to pick an AED without known major drug interactions or liver metabolism would be important in people with a risk of osteoporosis, in women of child-bearing age especially those on contraceptives, reproductive problems such as impotence in men, people on multiple other drugs (see above), the elderly who are already on other medication and to avoid systemic chronic side effects.

In conclusion, adverse effects of AEDs are important to recognize. It is the duty of the physician to be aware of potential AEs when dealing the AEDs. It is advantageous to remember that all AEDs are powerful neuromodulators so that side effects should be of no surprise. Vigilance is the most important aspect to remember when dealing with AEDs. Patients may not have the vocabulary to express how they

feel, so we professionals need to take all complaints seriously and try to deal with them as appropriately as possible.

Primary Reference:
Perucca P(1), Gilliam FG., Adverse effects of antiepileLorem Ipsen
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