AED side effects and how to minimize them

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MAJOR ANTIEMOTIONAL DRUGS: 2008

- Phenytoin
- Carbamazepine
- Sodium Valproate
- Phenobarbital
- Primidone
- Felbamatine
- Gabapentin
- Lamotrigine
- Topiramate
- Tiagabine
- Oxcarbazepine
- Levetiracetam
- Zonisamide
- Pregabalin
Is everyone prone to the same side effects?

- Side effects never happen to everyone
  - Some are common, some are very rare
  - Some will happen only in certain patient populations (children, elderly)
  - Some populations may be more vulnerable than others
    - Even in vulnerable populations, not everyone will have a side effect
  - Some only happen when the drug is used in a certain way
More Common side effects

- Dose-Related
  - May occur at any dose, but likelihood goes up as dose goes up
  - May happen when drug is used in a certain way (eg during titration)

- Psychiatric/Behavioral

- Body changes
  - Hormonal changes, bone changes

- Laboratory
  - Change in laboratory values
Rare Side effects

- Idiosyncratic
  - Very rare and unpredictable

- Teratogenic
  - Birth defects in children of mothers taking the drug
Relationship of AED Adverse Events to Quality of Life

N = 194
(r = -0.71, P<.0001)

Dose-Related Side effects-Case

- Mary is an 18 year old who has recently been diagnosed with epilepsy. She is taking Tegretol™ (carbamazepine)
- Seizures are not controlled, so her doctor adds Lamictal™ (Lamotrigine). Her doctor explains that it will take a few weeks to add the new drug to her regimen.
Dose-Related Side effects-Case

- At first Mary feels fine, but after a few weeks, when she is on Tegretol 400 twice a day and Lamictal 150 twice a day, she starts to feel unwell. She notices her concentration is “off”. She has to take a nap in the afternoon, and the most problematic issue is she gets double vision an hour after she takes her dose. However, she is not having seizures anymore!
Dose-Related Side Effects

- Unwanted physiologic effect of the drug on the brain
- Usually related to the Nervous system (difficulty concentrating, dizziness, unsteadiness, double vision)
- May happen at low doses, but more likely at high doses
- Once they happen, they tend to get more severe as the dose is increased further.
Dose-Related Toxicity: Older Drugs

- Dilantin™ (Phenytoin): ataxia, decreased concentration, fatigue
- Tegretol™ (Carbamazepine): ataxia, diplopia, decreased concentration, fatigue
- Depakote™ (Valproic acid): decreased concentration, tremor
Dose-Related Toxicity: Newer drugs

- Tends to be less than older drugs when used alone
- Can occur when combined with other drugs
### NEWLY TREATED:
**OLD AED vs NEW AED**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Lamotrigine (N=131)</th>
<th>Carbamazepine (N=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>30%</td>
<td>25%</td>
</tr>
<tr>
<td>Weakness</td>
<td>21%</td>
<td>29%</td>
</tr>
<tr>
<td>Nausea</td>
<td>23%</td>
<td>12%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12%</td>
<td>17%</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>12%*</td>
<td>22%* (sig)</td>
</tr>
<tr>
<td>Unsteadiness</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>Amnesia</td>
<td>6%</td>
<td>3%</td>
</tr>
</tbody>
</table>

From Brodie et al, Lancet 1995;345:476-9
Trileptal ™ (oxcarbazepine) Newly started: Drop-outs vs other drugs

- Tegretol (OXC₁) p = .002
- Depakote (OXC²) p = NS
- Dilantin (OXC³) p = .04

1. Guerreiro Epilepsy Research 1997
2. Christe Epilepsy Research 1997
3. Dam Epilepsy Research 1989
Dose-related side effects: new AEDs as add-on

<table>
<thead>
<tr>
<th></th>
<th>GPN</th>
<th>LTG</th>
<th>TGB</th>
<th>OXC</th>
<th>TPM</th>
<th>LEV</th>
<th>ZNS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dizziness</strong></td>
<td>10</td>
<td>25</td>
<td>12</td>
<td>20</td>
<td>14</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td><strong>Unsteadiness</strong></td>
<td>7</td>
<td>16</td>
<td>2</td>
<td>9</td>
<td>14</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td><strong>Speech / Language</strong></td>
<td>2</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td><strong>Double vision</strong></td>
<td>4</td>
<td>21</td>
<td>16</td>
<td>8</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What Can Mary’s Doctor Do?

- Seizure-free with dose-related side effects
  - Treatment: Tegretol™ (carbamazepine) 400 twice a day and Lamictal™ 150 twice a day
- Doctor can do several things that might reduce or even eliminate side effects without sacrificing seizure control
What Can Mary’s Doctor Do?

- Reduce/Eliminate Tegretol
- Change to Long-acting Tegretol
- Give Lamictal 100 three times a day

Any of these might eliminate the problem
## Combination side effects

<table>
<thead>
<tr>
<th></th>
<th>Lamictal as add-on (N=76)</th>
<th>Lamictal alone (N=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>20%</td>
<td>7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>16%</td>
<td>7%</td>
</tr>
<tr>
<td>Headache</td>
<td>13%</td>
<td>7%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>12%</td>
<td>2%</td>
</tr>
<tr>
<td>Coordination ABN</td>
<td>12%</td>
<td>2%</td>
</tr>
</tbody>
</table>

*Gilliam et al, Neurology 1998*
DOSING

More frequent dosing can keep blood level “in range”
What is the relationship of Blood Level to Dose-related side effects?

- Blood levels give an “average” range of the amount of medicine in the bloodstream that will be high enough to control seizures, but not high enough to cause dose-related toxicity.

- HOWEVER, individuals can react differently! Some people get side effects at low levels, and others feel fine at high levels.
“Therapeutic Range”

Risk of dose-related side effects

Risk of seizures

LEVEL

TIME

8  16  24
Psychiatric/Behavioral side effects

- Some drugs more likely to cause these than others
  - Irritability
  - Depression
  - Anxiety
  - Psychosis (rare)

- Other drugs may actually improve mood and behavior
Psychiatric/Behavioral side effects

- If there are psychiatric problems before starting a drug, the risk of problems is higher
- Sometimes psychiatric side effects are unpredictable
- Psychiatric side effects only affect a small proportion of people who start a drug (a few percent)
Drugs that are more likely to impact psychiatric function*

May Worsen
- Levetiracetam
- Topiramate
- Zonisamide
- Tiagabine
- Phenobarbital

May Improve
- Carbamazepine
- Valproate
- Lamotrigine
- Pregabalin (anxiety)

*This is only the most common-sometimes each can do the opposite!
Kids and behavior

- AEDs may cause behavior problems or hyperactivity in children
  - Phenobarbital, gabapentin, pregabalin, have been implicated, but any drug can have this effect.
What about suicidality?

- FDA recently released an advisory stating that in clinical trials of new AEDs, those in the drug-treated arm had a higher risk of suicidal thoughts than those in the “placebo” arm.
- According to the report, no drug was better or worse than any other.
Should you worry?

- Increase was less than half a percent
- These drugs also substantially improved seizures
- Risk outweighs the benefit
What should the treating doctor do to reduce risk of psychiatric side effects?

- Keep an open line of communication, and ask about mood effects.
- Warn patients that these effects may emerge when starting a new drug.
- If a drug is extremely effective, but causing mood or anxiety problems, it may be worth trying an antidepressant or antianxiety drug in combination with the AED.
Effects of AEDs on the body

- AEDs can have many effects on the body
  - Change hormones/vitamins
  - Change Bone density
  - Change weight
  - Increase the “speed” of metabolism
How do AEDs cause some of their effects?

- Liver metabolism
- Mechanism for drug handling by the body
- Many antiepileptic drugs influence liver metabolism
- Some will increase, some will decrease liver metabolism
WHAT CAN HAPPEN TO OTHER DRUGS?

- If other drugs are metabolized faster, there is less drug around to have an effect.
- This may lead to the drug being less effective!
- Drugs that can be affected include birth control pills, antidepressants, statins, bloodthinners and other common drugs.
AED LIVER METABOLISM

- Different substances all get broken down (metabolized) in the liver
  - Hormones
  - Drugs
  - Vitamins
- Once broken down, substances can leave the body
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- Different substances all get broken down (metabolized) in the liver
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  - Drugs
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- Once broken down, substances can leave the body
Vitamins can be affected by increased metabolism

Vitamin D
Important for bone health

Vitamin K
Important for clotting
DRUGS THAT INCREASE METABOLISM

- Phenytoin
  - Dilantin
  - Phenytek
- Carbamazepine
  - Tegretol
  - Tegretol XR
  - Carbatrol
- Phenobarbital
**BONE HEALTH**

- Less Vitamin D can lead to increased risk of bone thinning (osteoporosis)
- Increased risk of fracture
- Epilepsy already associated with fracture risk due to falls
- Compared with the general population: patients with epilepsy have a 3 fold higher risk for hip fractures and two-fold higher risk for all fractures
AEDs and bones

- Drugs that can increase metabolism of Vitamin D:
  - Dilantin (most implicated)
  - Tegretol, (Carbatrol, XR)
  - Phenobarbital

- Depakote may also cause bone thinning due to other mechanisms
BONE HEALTH

What can you do?

- Take Vitamin D and Calcium supplements up to 600/1500 mg
  - Oscal with D,
  - Viactiv
- Weight-bearing exercise
- Bone test as baseline and every few years
  - Dexascan-if osteopenia consider referral to specialist
- Other treatments for osteoporosis if needed
  - Biphosphonates
- Change in AED may be considered for significant osteoporosis
VITAMIN K

- Important vitamin for clotting
- Also metabolized through the liver
- Usually enough around, but during pregnancy, may need more
- If you are on Dilantin, Tegretol (Carbatrol, XR), phenobarbital, may need supplement during last month of pregnancy to prevent bleeding
HORMONES

- Hormones that can be affected by antiepileptic drugs:
  - Estrogen
  - Progesterone
  - Thyroid hormones
ESTROGEN

- Female hormone

- Metabolism can be sped up by:
  - Dilantin
  - Tegretol (XR, Carbatrol)
  - Phenobarbital

- Metabolism can be slowed down by:
  - Depakote
What happens when estrogen metabolism slows down?

- Depakote slows estrogen metabolism
- This and other effects of depakote may lead to central obesity, and polycystic ovarian syndrome
- Younger women more susceptible than old
- Potentially reversible when Depakote is stopped
Polycystic ovarian syndrome

- A group of symptoms including:
  - Hirsuitism
  - Obesity
  - Balding
  - Anovulatory cycles
  - Acne

- Polycystic ovaries are not necessarily seen!
Polycystic ovarian syndrome

- How common is PCO in women taking Depakote?
  - Up to 50% (but women with epilepsy overall have higher risk)
- What if you think you have PCO?
- Talk to your doctor
- Consider risk vs benefit of change to another AED
What happens when Estrogen metabolism speeds up?

- Less estrogen may have effects on sex drive, other body functions
THYROID HORMONE

- Only drug that affects is Tegretol (XR, Carbatrol)
- Thyroid function is usually not affected, but TESTs that measure thyroid function are!
- If your doctor is not aware, may misinterpret tests as showing hypothyroidism.
- If really hypothyroid, TSH as well as T3 and T4 are affected
CHOLESTEROL

- Tegretol ( XR, CARBATROL) may increase cholesterol level
- No evidence this increases cardiac risks
- Should you still take cholesterol lowering drugs?
  - Probably
WEIGHT

- Some antiepileptic drugs increase or decrease weight
- Only happens to a portion of those taking drug, not all.
ANTIEPILEPTIC DRUGS THAT AFFECT WEIGHT

INCREASE
Depakote
Neurontin
Tegretol
Lyrica
ANTIEPILEPTIC DRUGS THAT AFFECT WEIGHT

DECREASE
Topamax
Zonegran
What can you do about weight change?

- Ask your doctor about lowering the dose
- Taking a long-acting form (eg Depakote ER™) *may* help.
- Consider switching to another AED.
- Diet and exercise still work!
Idiosyncratic Side Effects

- Very rare, unpredictable
- Probably genetic predisposition
- Almost always will occur within 2 years of starting a new drug (and most within 6 months)
Major Idiosyncratic Adverse effects: Older AEDs

<table>
<thead>
<tr>
<th></th>
<th>Serious Rash</th>
<th>Liver Failure</th>
<th>Bone Marrow Failure</th>
<th>Pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tegretol™</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>(Dilantin™)</td>
<td></td>
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<tr>
<td>Phenobarbital</td>
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</tr>
<tr>
<td>Valproic Acid</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>Depakote™</td>
<td></td>
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</tbody>
</table>
Major Idiosyncratic side effects: New Drugs

- Felbamate (Felbatol™): Bone marrow failure, liver failure, serious rash
- Lamotrigine (Lamictal™): Serious rash
- Topiramate (Topamax™): Kidney stones, glaucoma, Heat stroke (Kids)
- Oxcarbazepine (trileptal™): Serious rash, ? Bone marrow failure, very low blood sodium
- Zonisamide (Zonegran™): Serious rash, Bone Marrow failure, Kidney Stones, Heat Stroke (kids)

- Levetiracetam (Keppra™), Gabapentin (Neurontin™), Pregabalin (Lyrica™): None reported so far.
Typical maculopapular rash
What can your doctor do to avoid idiosyncratic side effects

- Keep you informed of what signs or symptoms might be a warning of a serious problem (e.g., rash)
- Do routine blood tests, if necessary (sometimes a serious problem will be preceded by changes in laboratory tests such as blood counts and liver function tests)
- Not all idiosyncratic side effects can be avoided!
Conclusion

- It’s important to know how drugs may affect you
- If you think there is a problem, talk to your doctor
- Communication is key!