Proconvulsant Drugs and Aggravation by AEDs

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Overview

- A convulsant is a drug which induces or aggravates seizures, the opposite of an anticonvulsant.
- Over 10% if all AEDs, prescriptions in adults are associated with a simultaneous prescription of at least one proconvulsant drug.
- It is difficult to judge the appropriateness of the coprescription of proconvulsant drug but the high prevalence is worrying.
How drugs could induce seizures

- **Direct effects on the central nervous system**

  Disturbances of cerebral energy metabolism through:
  - stimulation of the CNS
  - neurotransmitter disturbances
  - chronic changes in alpha-2 receptors
  - cerebral cortical irritation
  - toxic effects on neurons

- **Indirect effects**

  - Cerebral blood flow disturbances
  - Cerebral hypoxia
  - Secondary to non-neurologic drug reactions:
    - cardiac rhythm disturbances
    - electrolyte disturbances, eg, hyponatremia, hypomagnesemia
    - metabolic disturbances, eg, hypoglycemia
    - fever
Antidepressants

- Not Surprisingly, Tricyclic antidepressant drugs and phenothiazines between them account for the vast majority of co-prescribed proconvulsant drugs.
- Depression is common in the general population and occurs even more often in patients with epilepsy (up to 50%, depending on the screening tool used).
- AEDs such as carbamazepine or valproic acid, may trigger depression or mania when discontinued, and barbiturates can initiate or exacerbate depression.

Serotonergic medicine causing Serotonin Syndrome

<table>
<thead>
<tr>
<th>Class</th>
<th>Specific names</th>
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<tbody>
<tr>
<td>Antidepressants</td>
<td>Mertazapine, MAO I, SSRI, TCA, Venlafaxine</td>
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<tr>
<td>AntiParkinson</td>
<td>Amantadine, Bromocriptine, Carbergoline, Levodopa, Pergolide, Selegline</td>
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<tr>
<td>Illicit Drugs</td>
<td>Cocaine, Hallucinogenic amphetamines such as MDMA (Ectasy), LSD</td>
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<td>Migraine Therapy</td>
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<tr>
<td>Other Agents</td>
<td>Buropion, Carbamazepine, Lithium, Morphine, Petidine, Reserpine, Tramadol</td>
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The risk of seizures in patients taking antidepressant drugs:
- The intrinsic epileptogenic or antiepileptic potential of the antidepressant
- The amount of active drug that enters the brain, which depends on the dose, pharmacokinetics, and transport across the blood-brain barrier
- The patient’s seizure threshold, which depends on genetic factors, remote brain injury, previous febrile or acute symptomatic seizures, and use of alcohol or other substances

Epileptogenic effects of antidepressants
- The complex neurotransmitter effects of antidepressant drugs make it impossible to offer simplistic assumptions about their proconvulsant effects
- It is unlikely that alterations in serotonin and norepinephrine levels are related to an increased risk of seizures.
- The antihistaminic, antimuscarinic, and local anesthetic properties of antidepressants that are most likely responsible for any increased susceptibility to seizures
- Even simple side effects of medication, however, such as drowsiness, can lower the seizure threshold in susceptible patients.
- Pharmacokinetic interactions with AEDs may interfere with their action and precipitate seizures
Which antidepressants increase seizure risk the most?

- Clomipramine heterocyclic antidepressant (0.5% incidence, up to 2.1% with doses of 350 mg per day or greater)
- the dopamine- or norepinephrine-specific reuptake inhibitor bupropion (0.4%, up to 2.2% with doses higher than 450 mg per day)
- the quaternary antidepressant maprotiline (0.4%)
- The tricyclic antidepressants (TCAs) have the next highest seizure risk (which is increased by toxic levels)
- The newer selective serotonin reuptake inhibitors (SSRIs) are intermediate in risk, as is venlafaxine, a combined norepinephrine and serotonin reuptake inhibitor.

Pharmacokinetic effects

- Enzyme-inhibiting antidepressant drugs, such as the SSRIs and TCAs, may require downward adjustment in the dosage of concurrently administered AEDs that are also metabolized by the cytochrome P-450 (CYP450) microsomal system in the liver.
- In other cases, phenytoin and carbamazepine inhibit the metabolism of antidepressant drugs, like fluoxetine or the TCAs, which leads to unintended toxicity from the antidepressant.
Electroconvulsive Therapy??

- Although isolated case reports have described spontaneous seizures after electroconvulsive therapy (ECT), an increased incidence has not been confirmed by larger series.
- A seizure disorder is no longer a contraindication to ECT.
- In patients with epilepsy who require ECT, maintenance AEDs should be withheld the day of treatment to obtain the best response.
- Newer technologies for treating depression, such as transcranial magnetic stimulation (TMS) and vagus nerve stimulation (VNS), have not been associated with any increased risk of seizures.

Antipsychotics

- The absolute number of seizures reported with antipsychotic drugs is less than with antidepressants, but this may reflect the smaller number of people using antipsychotics, rather than a difference in the epileptogenic potential of this class of drugs.
- The epileptogenic potential of antipsychotics depends somewhat on the ratio of D1 to D2 blockade, as well as the balance of glutamate and GABA activity. D1 agonists and D2 antagonists are proconvulsant.
- Clozapine, phenothiazines and butyrophenones carry a risk of 1%-4% of all patients.
- Seizures and EEG changes are depending on dose.
Tramadol

- Tramadol hydrochloride (marketed under the brand name the Ultram) is a centrally acting opioid analgesic used to treat moderate to moderately severe pain.
- Opioid activity is due to both law affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite μ1 to μ-opioid receptors (i.e., it inhibits reuptake of norepinephrine and serotonin. These mechanisms may contribute independently to the overall analgesic profile of tramadol.

- Seizures can occur with tramadol, particularly if high doses are used or if there is concomitant use of medicines that lower the seizure threshold. Seizures are strongly linked to the serotonin syndrome which triggered by tramadol.
- Increased cerebral serotonin activity by partial inhibition of its uptake.
Management
- The discontinuation of the causative agents with supportive treatment and the clinical symptoms and signs usually resolve within 24 hours.
- Hyperthermia should be treated with active cooling
- Rigidity, seizures and agitation should be treated with Benzodiazepines. Severe symptoms have been treated successfully with cyproheptadine 5-HT2 Antagonist.

Anesthesia
- General Anesthesia
  - Rapid induction of anesthesia occasionally can be associated with one or more acute seizures.
  - Propofol, flurane (a substitute for halothane), and benzodiazepines (especially lorazepam) seem to be the agents implicated most often.
Local Anesthesia

- Local anesthetics, Lidocaine, bupivacaine and procaine can induce seizures.
- Seizures occurring shortly after injection of moderate to large amounts of a local anesthetic should raise suspicion that the drug has been inadvertently introduced into the vascular supply. This is especially common with pelvic or oral surgery.

Baclofen

- Early clinical studies suggested that baclofen might be a proconvulsant and could exacerbate epilepsy. However, two prospective studies found that baclofen neither increased seizure frequency in epilepsy patients.
- Baclofen is not contraindicated in epilepsy patients, but it should be tapered gradually.
- Baclofen may suppress epileptiform activity in the hippocampus at concentrations below those that suppress normal synaptic transmission.
- Several reports suggest that baclofen may reduce myoclonus in epilepsy patients.
- Abrupt cessation of sustained treatment should be avoided, because sudden withdrawal of baclofen may cause hallucinations, psychosis, visual disturbances, and seizures.
Interleukin -1B (IL – 1B)

- IL – 1b is over produced in human and rodent epileptogenic tissue and it exacerbates seizures upon brain application in rodents.
- The proconvulsive IL – 1B effect is associated with increase Tyrophosphorylation of one of its substrates, the NR2 B subunit of the N – Methyl – O – aspartate receptor, which prevented by 3 – O – MS and CGP/76030 if enprodil (selective NR2 B receptor antagonist)

Anti Asthmatics

- Aminophylline and theophylline
- Especially but not exclusively above therapeutic levels
- They begin with focal motor seizures with or without secondary generalization and are followed by stupor or coma.
- The electroencephalogram typically shows periodic lateralized epileptiform discharges (PLEDS), which may provide a diagnostic clue.
- They are responsive only to adjustment of theophylline dosage.
Antibiotics

The exact incidence of seizures complicating antibiotic use is not known. Interpretation of empiric studies and meta-analyses of seizure complications of antibiotic use is complicated by the fact that patients given antibiotics often have other seizure risk factors, making it difficult to attribute the cause of seizures to the antibiotic. For example, the background seizure rate in seriously ill patients likely to receive intravenous antibiotics could be as high as 4%.

Penicillins

Epileptogenic characteristics of beta-lactams, like their antimicrobial and antigenic properties, are structure-dependent. The beta-lactam ring is a key feature of penicillin epileptogenesis, and convulsant properties are abolished after incubation with penicillinase.

It is thus not surprising that this class of drugs and its derivatives (e.g., imipenem) have been suspected of increasing the potential for seizures.
**Carbapenims**

- The proconvulsive activity of imipenem appears to increase when it is used in combination with cilastatin. This could be due merely to elevated imipenem levels in the presence of cilastatin.
- Comparison data indicated that seizures occurred no more frequently during treatment with meropenem than during treatment with other beta-lactam antibiotics.

**Fluoroquinolones**

- Proconvulsant effects of quinolones have been attributed to direct pharmacodynamic effects and to pharmacokinetic and dynamic interactions with co-administered drugs.
- Direct pharmacodynamic proconvulsant mechanisms of quinolones may relate to gamma-aminobutyric acid (GABA)-like substituents, which act as GABA-receptor antagonists.
Anti mycobacterial

- Overdosage of isoniazid (INH) precipitates seizures
- as early as 3 hours after ingestion.
- INH-induced seizures must be treated with pyridoxine (vitamin B6) in addition to antiseizure drugs.
- In this situation, anticonvulsants that are not metabolized in the liver should be used if possible, because INH also causes hepatic failure, thus leading to unpredictable drug levels and neurotoxicity.

AntiVirals

- Antiviral drugs (e.g., acyclovir, ganciclovir) are used to treat encephalitis, which in itself causes seizures.
- Dideoxyiodinase and zidovudine, standard treatments for patients infected with human immunodeficiency virus (HIV), are said to increase seizure risk
- Valproate stimulates HIV viral replication directly
Antifungal

- Antifungal and antimycobacterial drugs generally do not provoke seizures, although the severe shivering that can accompany amphotericin infusion can sometimes be confused with seizure activity.

Over the Counter and herbal medicine

- Pseudoephedrine, pheniramine, and other over-the-counter (OTC) antihistamines are associated with seizures, especially in overdose.
- Antihistamines, lower seizure threshold and should therefore be avoided, although the magnitude of this risk is not known.
- In one series, overdosage with diphenhydramine was the third leading cause of seizures.
Oral Contraceptives

- Less than half of the women on enzyme inducing AEDs are on a high estrogen content contraceptive pills.
- The Efficacy of the pill is reduced by enzyme inducing AEDs and women who are on such AEDs should not be prescribed low dose preparations.

Other Agents

- anticholinergics
- anticholinesterases
- lithium
- mefenamic acid
- insulin
- oral hypoglycemic
- heavy metals
- hyperbaric oxygen
- prednisone
- estrogen
The possibility that so-called anti-epileptic drugs (AEDs) may aggravate epilepsy must always be borne in mind by the clinician. Many reports of such aggravation of seizures have been published. Seizure aggravation may include increase in the frequency or severity of existing seizures, emergence of new types of seizure, or the occurrence of status epilepticus.
Pathophysiology

- The pathophysiology of seizure aggravation is poorly understood including nonspecific effects such as those associated with sedation, drug-induced encephalopathy, and paradoxical or inverse pharmacodynamic effects.

AEDs can aggravate epilepsy in several ways

- Without increase in seizures
  - Unreliable diagnosis, refusal/social limitations, quality of life

- With increased seizures through
  - Over dosage (or paradoxical intoxication),
  - inappropriate drug choice,
  - paradoxical reaction,
  - AED-induced encephalopathy
Overdosage (paradoxical intoxication)

- This is probably the most commonly observed reason for seizure aggravation.
- It is more likely to occur in children with severe and refractory epilepsy who are often on polytherapy.
- Usually other adverse effects are overt, such as sedation, irritability, or sleep disturbance.
- Experience suggests that such a response is more likely in patients on polytherapy; this is probably the main mechanism by which polytherapy can make seizures (and other adverse effects) worse.

Overdosage (paradoxical intoxication)

- Phenytoin (non linear kinetics)
- Carbamazepine (epoxide metabolite)
- Valproate (de novo myoclonic)
- Lamotrigine (de novo myoclonic)
Inappropriate AED Choice

- Carbamazepine use in absence, atypical absence, myoclonic, and atonic, Absence > Absence status after introduction of CBZ
- Ethosuximide: Reports attributing aggravation of generalized convulsive seizures to ethosuximide
- Phenobarbital: Absence seizure exacerbation and the possible triggering of absence status have been reported
- Lamotrigine: Pronounced seizure deterioration of severe myoclonic epilepsy.

Seizure worsening related to paradoxical reaction

- A paradoxical reaction occurs when an AED appears to exacerbate a type of seizure against which it is usually effective, or when it leads to the onset of new types of seizures. This unpredictable adverse effect usually occurs shortly after introduction of the AED at nontoxic serum levels.
- Childhood epilepsy syndromes with multiple seizure types pose a special problem because they appear to be particularly prone to paradoxical reactions.
Carbamazepine: The majority of paradoxical reactions reported in children are related to this AED. Episodes of generalized convulsive status epilepticus were reported to have been triggered children who were being treated with add-on CBZ for “mixed seizure disorders”.

Benzodiazepines: In several reports, i.v. benzodiazepines (BDZs) [nitrazepam, diazepam, lorazepam, (CZP) clonazepam] have been correlated with precipitation of tonic status epilepticus in patients with LGS. In most of these patients, BDZs had been administered for treatment of absence status.

3 years old, Benign Rolandic Epilepsy, and Epileptic Negative Myoclonus On Valproate and Carbamazepine
The same Patient, one month after withdrawal of Carbamazepine

- **Vigabatrin**: De novo appearance of myoclonic jerks was described in several reports on children or young adults with cryptogenic or symptomatic partial epilepsy treated with add on VGB.
- **Levitracetam** (reports of small number, Absence and apneic episodes)
- **Lamotrigine**: It has been associated with seizure aggravation in several epilepsies. These include the appearance of absence seizures in Benign Rolandic Epilepsy with Central Temporal Spikes (BECTS), myoclonic status in high doses, and deterioration of seizures in Severe Myoclonic Epilepsy.
- **Topiramate**: Early studies of topiramate suggest that aggravation of pre-existing seizure types occurs in 4 to 6% of children, however, no specific association has yet emerges.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Epilepsy/Seizure</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Carbamazepine</td>
<td>BECTS Absences JME, PME ESES</td>
<td>ESES Increase Myoclonic Global Aggravation</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Absences ESES PME</td>
<td>Risk of increase global Aggravation</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Absences</td>
<td>Increase (high doses)</td>
</tr>
<tr>
<td>Vigabatrin/Gabapentin</td>
<td>Absences Myoclonias</td>
<td>Increase Increase</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>SME JME</td>
<td>Aggravation</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Focal Epilepsies</td>
<td>Increase (10% of cases)</td>
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Worsening of seizures during AED-induced encephalopathy

- Seizure aggravation may be associated with some forms of AED-induced encephalopathy. When aggravation accompanies encephalopathy secondary to toxic levels, a paradoxical intoxication is considered to have occurred.
- Valproate, either in monotherapy or, more often, in poly therapy, can produce encephalopathy with seizure exacerbation, with or without altered hepatic function.
- Children present with nausea, vomiting, apathy, seizure increase, slowing in background EEG activity, and increase in paroxysmal discharges, accompanied by laboratory signs of hepatic failure.
- Also reported with Carbamazepine
HOW DO WE KNOW THAT THE DRUG IS RESPONSIBLE FOR THE AGGRAVATION?

- there are several features that should attract the clinician’s attention and raise the possibility of true pharmacodynamic aggravation
  - There is a close time relationship between the introduction of the drug and the increase of seizure activity; there is also globally a relationship between the dose and the aggravating effect.
  - New seizure types may occur together with the exacerbation of the usual seizures, i.e., atypical absences and drop attacks in BECTS.
  - There is no marked associated side effect, and no symptom of metabolic or encephalopathic complication.
  - There is usually an increase of paroxysmal interictal EEG changes, and only a slight change of the background activity.
  - The onset of aggravation is quick, and may only be delayed in such cases where the increase of dosage is very slow.

WHAT TO DO WHEN SEIZURE WORSENING OCCURS?

- Check the absence of other mechanisms of aggravation, including overdosage (blood levels of the AED should be within the usual range), lack of compliance and metabolic or encephalopathic complications, using the relevant procedures.
- Reassess the diagnosis of epilepsy. If seizures have become particularly frequent, it may be the right time to perform a video-EEG ictal recording. If the precise diagnosis remains doubtful, be careful in prescribing other drugs.
- Withdraw the incriminated drug. Such withdrawal may be rapid in case of a very recently introduced compound, and the replacement drug can also be introduced according to a short cross-over design.
- Rechallenge with the culprit AED may be tried in selected cases, under close clinical and EEG supervision.
Conclusion

- You may worsen your patient’s Epilepsy using the wrong AED
- It happens to the best and the brightest
- Pharmacosensetivity is characteristic with many epileptic syndromes
- AEDs with broad spectrum are less likely to produce aggravations
- Your patient is aware of this before you are: Listen to this “dislike” of any given AED

- Patients on AEDs might be on co-prescribed medication which could have adverse interactions has proved to be justified
- Prescribers should be alert to the possibility of pharmacodynamic and pharmacokinetic interactions between AEDs and other medications
- With the aging of the population of people with seizures and the polypharmacy often associated with old age, the likelihood of adversely interacting drug combinations will increase
- In cases where patient’s seizures seem difficult to control, the possibility for co-prescription of a proconvulsant drug should be entertained.