Lowering the seizure threshold associated with antidepressants, stimulants, antipsychotics, and others

Caleb Y. Oh, Pharm.D.
Jacquelyn Bainbridge, Pharm.D., FCCP

ABSTRACT

While seizures are commonly associated with epilepsy, seizures can also be provoked by many other causes, including trauma, stroke, fever, and medications. The seizure threshold refers to the patient's susceptibility to seizures. This article reviews common psychiatric medications which may alter the seizure threshold.

KEYWORDS

seizure, seizure threshold, antidepressant, stimulant, antipsychotic

Each year, 120 people per every 100,000 of the U.S. population seek medical attention due to a new seizure experience.[1] However, not everyone that experiences a seizure has epilepsy, as epilepsy is defined as having recurrent, unprovoked seizures.[1] Seizures can be provoked by various causes including, but not limited to trauma, stroke, fever, and medications. The seizure threshold describes a balance that exists between excitatory and inhibitory signals in the brain. The exact threshold to provoke a seizure varies from person to person.[2] A high concentration of excitatory signals and/or a low concentration of inhibitory signals increases a person's susceptibility to seizures. This coincides with many mechanisms of antiepileptic drugs (AEDs) in that they either potentiate inhibitory signals (GABA) or decrease excitatory signal (glutamate) conduction via various ion channels.

Though pharmaceutical manufacturers often try to develop drugs that will not interfere with other medications, it is not always feasible. This quandary puts a vital responsibility on pharmacists and other health care practitioners to create safe and efficacious drug regimens for patients. Seizures in any form can produce damage in the brain and decrease the patient's quality of life. Understanding which drugs can alter the seizure threshold and avoiding their use in high risk patients can potentially prevent recurrent seizures, or avert an event altogether. Many medications have been associated with seizures, but this article will focus on specific classes commonly used in psychiatry.

ANTIDEPRESSANTS

Bupropion is commonly associated with lowering of the seizure threshold. This effect appears to be dose-related and can potentially be avoided if the dose is titrated slowly and does not exceed 450 mg/day. If possible bupropion should be avoided in patients with a known diagnosis of epilepsy. Tricyclic antidepressants (TCAs), at supratherapeutic doses can induce seizures. TCAs can block $GABA_A$ receptors and decrease inhibitory neuronal signals, resulting in seizures.[3] Caution should be exercised when using these medications in patients who may be at a high risk of developing seizures or have a known diagnosis of epilepsy. If TCAs are prescribed they should be titrated slowly and patients should be monitored for adverse events. A rare side effect of selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) is serotonin syndrome, which can lead to seizures in 1- 2 % of affected patients, and is extremely rare.[4] Use of SSRIs and SNRIs should not be withheld in patients with epilepsy.

STIMULANTS

Stimulants such as amphetamine, dextroamphetamine, and methylphenidate are commonly prescribed to treat Attention Deficit Disorder (ADD) and Attention Deficit/Hyperactivity Disorder (ADHD) in children as well as adults. Other uses of stimulants include treatment of fatigue and daytime somnolence. Stimulants can make existing seizure disorders worse, but rarely cause seizures in patients without a history of seizures. A postulated mechanism of seizure activity due to this class of medications may be associated with increased catecholamine release causing excitatory stimulation. Excess catecholamine release can precipitate seizures via loss of sleep and physical stress.

ANTIPSYCHOTICS

All antipsychotics can lower the seizure threshold. However, the antipsychotic that is most often associated with seizures is clozapine. Clozapine lowers the seizure threshold in a dose-dependent fashion. As the dose increases, the risk of side effects increases significantly. A clozapine dose of 300-600 mg/day resulted in a seizure

incidence of 1.8% and doses greater than 600 mg/day showed a seizure incidence of 4.4%.[5] Escalation of the clozapine dose should be done slowly, and the serum level should be obtained before exceeding a 600 mg/day dose.[6] If a drug induced seizure occurs during therapy, the practitioner should switch to risperidone, molindone, thioridazine, haloperidol, pimozide, trifluoperazine, or fluphenazine. These antipsychotics are less likely to affect the seizure threshold.[6] If the patient cannot be switched off of clozapine then an AED (valproate, lacosamide, etc.) can be initiated and the patient monitored for adverse effects. Levetiracetam would not be the best choice because it can precipitate psychosis.

OTHER DRUGS ASSOCIATED WITH LOWERING THE SEIZURE THRESHOLD

This is not an exhaustive list of medications or drug classes that in the past have demonstrated a potential lowering of the seizure threshold.[6] A few drugs that stand out as more commonly precipitating seizures are: baclofen upon abrupt discontinuation high dose, dalfampridine, and tramadol.

- Acetylcholinesterase inhibitors
- Anticholinergics
- Antiemetics
- Antihistamines
- Baclofen
- ß-Blockers
- Cephalosporins
- Cyclosporine
- Dalfampridine
- Estrogen
- Imipenem
- Iodinated Contrast Dyes
- Isoniazid
- Lithium
- Local anesthetics
- Methotrexate
- Metronidazole
- Narcotics
- Penicillins
- Pyrimethamine
- Quinolones
- Tacrolimus
- Theophylline
- Tramadol

Recognizing patients who are at increased risk of seizures is as important as realizing which drugs lower the seizure threshold. Certain conditions that increase the risk of seizures include head trauma, brain tumor, stroke, intracranial infection, anorexia nervosa, and other congenital abnormalities. In addition to many conditions that increase the risk of seizures, the pharmacist must realize their importance in recognizing medications that can lower the seizure threshold. Nevertheless, it is important to realize that each new seizure must be evaluated carefully. Though a drug may appear to be the most likely cause of a new seizure, there may be other underlying causes.

REFERENCES

1. Rogers SJ, Cavazos JE. Epilepsy. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: A Pathophysiologic Approach. 8th ed. New York, NY: McGraw-Hill; 2011:979-989.
2. Seizure Threshold. Epilepsy Foundation. Landover, MD http://www.necfoundation.org/organizations/organizations_show.htm?doc_id=135389. Retrieved 2012/10/24.
3. Hutchinson MD and Traub SJ. Tricyclic Antidepressant Poisoning. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2012.
4. Ganetsky M. Selective Serotonin Reuptake Inhibitor Poisoning. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2012.
5. Levin M and Burns MJ. Antipsychotic Agents. In: Shannon: Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose, 4th ed. Philadelphia, PA: Saunders; 2007:712
6. Crismon ML, Argo TR, and Buckley PF. Schizophrenia. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: A Pathophysiologic Approach. 8th ed. New York, NY: McGraw-Hill; 2011:1162
7. Bainbrdige, J. Epilepsy and Headache/Migraine. In: Ambulatory Care Pharmacy Preparatory Review Course Vol. 1. Lenexa, KS; ACCP; 2011:210

How to cite this editor-reviewed article
Oh CY, Bainbridge J. Lowering the seizure threshold associated with antidepressants, stimulants, antipsychotics, and others. Ment Health Clin [Internet]. 2012;2(5):127-8. Available from: http://dx.doi.org/10.9740/mhc.n127568