Anticonvulsant effects of SSRIs

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ABSTRACT

Although it has previously been thought that serotonin reuptake inhibitors (SSRIs) increase seizure risk, recent evidence suggests that the risk of seizures comes from an underlying deficiency in serotonin rather than the pharmacologic treatment. This article reviews some of the theories on the mechanisms behind seizures, and how antidepressant therapy, particularly SSRIs, could affect the risk.

KEYWORDS

depression, epilepsy, selective serotonin reuptake inhibitor (SSRI), seizure

The incidence of depression is more common in patients with epilepsy compared to the general population.[1] Treatment of comorbid depression is recommended over watchful waiting given the elevated rates of suicide in this patient population.[2] In January of 2008, the Food and Drug Administration (FDA) reported that many antiepileptic drugs (AEDs) are associated with an increased risk for suicidality, further warranting timely treatment of depression.[3] However, epilepsy patients with depression have often been undertreated due to the misconception of an association between antidepressants and seizure activity. Although it has previously been thought that serotonin reuptake inhibitors (SSRIs) increase the risk for seizures, more recent evidence suggests that the seizure risk comes from the underlying deficiency in serotonin rather than the pharmacologic treatment. In other words, depression itself is associated with lowering the seizure threshold.

Seizures can occur from many mechanisms, known and unknown. Theories regarding deficiencies in gamma-aminobutyric acid (GABA) and excess glutamate have lead to the development of pharmaceutical therapies which enhance GABA and attenuate glutamate to decrease or abort seizure activity in many patients. Other currently available medications for the treatment of epilepsy target sodium channels, potassium channels, and/or calcium channels. Blockade of sodium channels prevents the depolarization of action potentials to reduce neurotransmission while opening of potassium channels slows the repolarization of action potentials, also to reduce neurotransmission. Inhibiting calcium channels prevents the influx of calcium into the presynaptic vesicle and thus, the release of neurotransmitters into the synaptic cleft. These mechanisms have also shown to be beneficial for the treatment of epilepsy in some patients.

In addition to these mechanisms, serotonin, also known as 5-hydroxytryptamine (5-HT), may also play a role. Current literature demonstrates that loss of 5-HT lowers the seizure threshold, predisposing patients to seizures.[4] Patients with epilepsy are deficient in both pre- and post-synaptic serotonergic transmission with reduced binding to 5-HT receptors in multiple areas of the brain.[4] Similar deficiencies have been observed in patients with psychiatric disorders such as depression.[5] Potentiating serotonergic activity results in an improvement in mood as well as anticonvulsant effects.[4]

Some currently available AEDs appear to have serotonergic properties. Carbamazepine reduces the rapid firing of action potentials by enhancing the effects of GABA inhibitory neurotransmitters and increases serotonergic transmission as an additional mechanism of action.[4] The significance of this mechanism was demonstrated in rat studies when the anticonvulsant property of carbamazepine was greatly reduced following treatment with a serotonin synthesis inhibitor.[4] Other AEDs, including lamotrigine, valproate, and zonisamide, have also demonstrated serotonergic anticonvulsant mechanisms in animal studies.[4] Lamotrigine has demonstrated inhibition of serotonin reuptake ***in-vitro*** in human tissue as well.[4]

The significant increases in 5-HT within the extracellular fluid of the brain following treatment with SSRIs are associated with anticonvulsant effects. Literature evaluating the use of SSRIs for the treatment of epilepsy in humans is limited. Fluoxetine 20 to 80 mg, sertraline 25 to 200 mg, paroxetine 20 mg, and citalopram 20 mg daily appear to be safe as adjunctive therapy to AEDs in patients with epilepsy and depression.[6-8] In one study, the addition of fluoxetine 20 mg daily reduced seizure frequency by 30% and six patients who experienced daily seizures prior to therapy were seizure-free for the last

eight months of the study.[4,9] The addition of citalopram was tested in 11 epilepsy patients without depression and the median seizure frequency was reduced by 56%.[4] In rat studies, sertraline provided reductions in the severity of generalized tonic-clonic seizures as well as secondarily generalized seizures.[4]

Serotonin also plays a role in respiration. Respiratory depression and subsequent increases in carbon dioxide (CO_2) levels can be seen as a result of generalized convulsive seizures.[10] Without resuscitation, respiratory arrest and cardiac arrest may occur. Serotonin enhances respiration in response to elevated CO_2 levels.[10] SSRIs increase the availability of 5-HT to prevent these events and reduce the risk of sudden unexpected death in epilepsy which occurs in up to 17% of epilepsy patients.[10]

Although it is thought that some antidepressants increase glutamatergic neurotransmission, which could cause convulsions, SSRIs reduce the potassium-evoked release of glutamate and provide anticonvulsant properties.[4] However, at large doses, these drugs may act as convulsants and induce seizures.[4] Some antidepressants have effects on G-protein coupled K^+ channels and inhibition of these channels prevents repolarization of action potentials.[4] Others, including SSRIs, may increase expression of brain-derived neurotrophic factor, a neuronal growth factor which enhances synaptic transmission at excitatory synapses.[4] Additionally, histaminergic neurons suppress seizures and histamine H_1 receptor antagonists have proconvulsant effects on humans. This inhibition of histamine may explain the increase in seizure risk with tricyclic antidepressants, which have the greatest epileptogenic effect among antidepressants, despite their ability to improve serotonergic deficiencies.[4] These mechanisms may contribute to the generation of seizures, but there is currently insufficient evidence to determine which mechanisms are responsible for the convulsant properties of particular antidepressants and these mechanisms are not likely to be identical for all antidepressants.

The potential for SSRI-induced seizures is very low.[4] Antidepressant doses which are known to causes seizures in humans are much larger than those used clinically.[4] For example, studies assessing the safety of citalopram found that high doses (50 mg/kg) have been associated with convulsions, but 40 mg is the maximum daily dose recommended by the FDA.[11]

Some SSRIs may interact with AEDs. Caution should be exercised when fluoxetine or fluvoxamine are used concomitantly with AEDs.[2] These medications may cause an increase in AED serum levels by inhibiting AED metabolism.[2] Another consideration is the long half-life of fluoxetine. The international consensus statement for the treatment of neuropsychiatric conditions associated with epilepsy recommends SSRIs as first line for the treatment of interictally diagnosed depression due to the low seizure risk and high tolerability associated with these agents.[2]

Depression and seizures have a bidirectional relationship; depression is a risk factor for seizures and seizure control is greater if depression is treated.[5] Deficiencies in 5-HT are seen in depression and in epilepsy. Patients with depression have a six-fold increase in the risk for seizures and exacerbations of seizure activity can be attributed to the underlying affective disorder, rather than the antidepressant therapy.[4] For years, the serotonergic anticonvulsant mechanism has been overlooked. SSRIs have the potential to be effective AEDs as 5-HT plays a protective role in the central nervous system. To date, no large, randomized clinical trials in humans have been conducted on the use of SSRIs for the treatment of epilepsy. Further investigation is required to confirm the anticonvulsant properties of SSRIs and evaluate the efficacy of these agents as monotherapy. Additional studies are also needed to determine which mechanisms contribute to the convulsant and anticonvulsant properties of SSRIs.

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