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Frank Gilliam

Hrvoje Hećimović

Matthew S. Gentry

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## Serotonergic Therapy in Epilepsy

Frank G. Gilliam, MD, MPH<sup>1</sup>, Hrvoje Hecimovic, MD, PhD<sup>2</sup>, Matthew S. Gentry, PhD<sup>3</sup>

<sup>1</sup>Department of Neurology, University of Texas Rio Grande Valley

<sup>2</sup>Zagreb Neurocenter and University North

<sup>3</sup>Department of Molecular and Cellular Biochemistry, University of Kentucky

### Abstract

**Purpose of review**—The serotonergic system is implicated in multiple aspects of epilepsy, including seizure susceptibility, sudden unexpected death in epilepsy (SUDEP), and comorbid depression. Despite the complexity of serotonin’s effects on various neuronal networks, ongoing research provides considerable insight into the role of serotonin in human epilepsy. This review explores the potential roles of serotonergic therapies to improve clinical outcomes in epilepsy.

**Recent findings**—In recent decades research has markedly increased our knowledge of the diverse effects of serotonin on brain function. Animal models of epilepsy have identified the influence of serotonin on seizure threshold in specific brain regions, serotonergic augmentation’s protective effects on terminal apnea and mortality in SUDEP, and mechanisms underlying behavioral improvement in some models of comorbid depression. Human clinical studies are largely consistent with animal data, but the translation into definitive treatment decisions has moved less rapidly.

**Summary**—Evidence for serotonergic therapy is promising for improvement in seizure control and prevention of SUDEP. For some epilepsies, such as Dravet syndrome, basic research on serotonin receptor agonists has translated into a positive clinical trial for fenfluramine. The cumulative results of safety and efficacy studies support the routine use of SSRIs for comorbid depression in epilepsy.

### Keywords

epilepsy; serotonin; 5-hydroxytryptamine; SUDEP; depression

### Introduction

Serotonin, also known as 5-hydroxytryptamine, is a biochemical messenger and regulator synthesized from the essential amino acid L-tryptophan. It was initially described as enteramine in 1937 by Dr. Vittorio Erspamer while studying smooth muscle constrictors of the gut. In 1952 enteramine was demonstrated to be the same substance that Drs.

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Contact Information: Frank G. Gilliam, MD, MPH, Professor – Department of Neurology, School of Medicine, University of Texas Rio Grande Valley, 2102 Treasure Hills Blvd, Harlingen, TX, Phone (956) 296-1538, frank.gilliam@utrgv.edu.

**Conflicts of Interest:** None

Irvine Page, Maurice Rapport, and Arda Green had called serotonin in their research on vasoconstrictors(1, 2). Serotonin was identified as a neurotransmitter in mammalian brains in 1953 by Dr. Betty Mack Twarog(3). After observing the structural similarity of serotonin and LSD, Dr. D.W. Woolley hypothesized the relationship between mental illness and serotonin in the 1950's; he further observed that injection of serotonin antagonists into mice "calls forth convulsions much resembling those of human epilepsy (3)." Dr. Page later summarized in his book *Serotonin* that "the great variety of suggested roles can be said to be a tribute to man's ingenuity and his unquestionable willingness to write papers...clearly, the field has fallen heir to the current disease of science- too many journals, too many meetings, and too little worth talking about(4)." Despite overestimates of some of the biological roles of serotonin, evidence supporting the association of serotonin and epilepsy has grown rapidly with a greater than five-fold increase in annual publications since 1990 as shown in figure 1. This paper reviews the growing understanding of the modulation of neuronal excitability by serotonin, and highlights recent publications on potential positive effects of serotonergic drugs on seizures, SUDEP, and depression in epilepsy(5).

### **Serotonin modulates neuronal excitability**

Serotonergic cell bodies of the nervous system are predominantly located in the raphe nucleus, and project to the medulla and spinal cord, cerebellum, limbic system and striatum, and cerebral cortex. Although serotonergic neurons represent less than 1% of all neurons in the brain, they exhibit diverse effects through complex mechanisms involving seven identified subtypes of G-protein-coupled receptors, 5HT<sub>1A-1F</sub>, 5HT<sub>2A-2C</sub>, 5HT<sub>3</sub>, 5HT<sub>4</sub>, 5HT<sub>5A-5C</sub>, 5HT<sub>6</sub> and 5HT<sub>7</sub>(6, 7). Clinically these effects have been found to regulate at varying degrees sleep, memory, reward, pain, appetite, sexuality, movement, mood, and seizure susceptibility(6). The mechanisms of serotonin's effects are multifaceted, with some receptor subtypes hyperpolarizing and others depolarizing neuron membranes involving glutamatergic or GABAergic neurons(8). For example, activation of 5HT<sub>1A</sub> receptors causes hyperpolarization of neurons in the hippocampus, whereas 5HT<sub>7</sub> may augment depolarization in certain neurons(9). The specific effect of serotonin on excitability and subsequent seizure susceptibility, mood, or respiration therefore depends on the subtype of 5HT receptors and types of neurons (e.g., pyramidal versus interneuron) that are involved, and these effects can vary by brain region.

### **Serotonergic drugs inhibit seizures**

In 1957 Bonnycastle et al proposed a relationship between serotonin and epilepsy inhibition based on the observation that many antiseizure medications increase the concentration of serotonin in rodent brain(10). Cerebrospinal fluid studies found elevated markers of serotonin metabolism in patients with epilepsy that were being treated with epilepsy medications compared to untreated patients and non-epilepsy controls; serotonin levels were highest in patients on toxic medication doses(11). Early mouse experiments demonstrated that intracranial injection of serotonin protected against pentylenetetrazol and audiogenic seizures, similar to the protective effect of GABA(12). However, initial investigations of electroshock seizures did not find that serotonin modulated seizure thresholds(13). Subsequent studies with other models such as pilocarpine-induced status epilepticus and

kainic-acid have demonstrated that serotonergic drugs reduce seizure frequency in chronic epilepsy(14, 15). Confusion has occurred due to reports that some tricyclic antidepressants with serotonergic mechanisms lowered the seizure threshold, but investigations of specific tricyclic drugs in primates such as photosensitive baboons concluded that the seizure effects were not due to serotonin system augmentation(16). More recent studies of serotonergic effects in rodent epilepsy models have demonstrated significant reduction in seizures(17, 18), including optogenetic activation of serotonin neurons in the dorsal raphe nucleus(19).

Despite the antiseizure effects of serotonin and related agonists, no antiseizure medications approved by the FDA have had serotonergic effects as their primary mechanism of action. However, several early clinical observations suggested that serotonergic drugs may reduce seizures(20–22). The development of fenfluramine, which increases serotonin release and inhibits transporter re-uptake, has provided strong pharmacological evidence for serotonergic therapy efficacy for epilepsy(23). Aicardi and Gastaut initially used fenfluramine for self-induced absence seizures based on “some success from a variety of psychiatric disorders,” reporting the ablation of a photoconvulsive response in a small series(24). Several subsequent observational studies supported efficacy of fenfluramine for children with encephalopathy and severe epilepsy, including repeated challenges due to drug shortages(25–28). Several children participating in these studies were confirmed to have *SCN1A* mutations, which initiated interest in serotonergic therapies for seizures in Dravet Syndrome(29).

The observational and experimental studies of seizure inhibition by fenfluramine culminated in a randomized, blinded, placebo-controlled trial for seizures in Dravet Syndrome(30). The 14-week trial demonstrated a median reduction of motor seizures of 74.9% in the 0.7 mg/kg fenfluramine group, 42.3% in the 0.2mg/kg fenfluramine group, and 19.2% in the placebo group. Both fenfluramine groups had significant seizure reductions compared to placebo ( $p<0.0001$  and  $p<0.02$ ). As anticipated by the serotonergic effects in the brain and gut, the most frequent adverse effects were decreased appetite, diarrhea, fatigue, and somnolence. Echocardiography did not find evidence for valvular dysfunction or pulmonary hypertension. Similar efficacy and safety results were obtained in a small prospective, open-label pilot study of Lennox-Gastaut syndrome(31).

Multiple additional drugs modulating serotonin signaling, including clemizole, locaserin, and trazodone, have emerged as antiseizure treatments for Dravet syndrome and possibly other epilepsies. Zebrafish with *SCN1A* homologue mutations develop motor seizures that have been used for phenotypic screening of drug libraries(32). Baraban and colleagues published a series of studies demonstrating that serotonin receptor agonists inhibit seizures in a zebrafish model of Dravet syndrome, which they have translated into small clinical studies that provide preliminary support for the antiseizure efficacy of lorcaserin(33). Their zebrafish Dravet model also allowed development of receptor binding affinity models of 28 analogues of clemizole; three of these analogues had serotonin receptor binding that exerted strong antiepileptic activity(34). These studies provide powerful support that 5HT<sub>2B</sub> agonists inhibit neuronal hyperexcitability and seizures in a disease caused by a specific sodium channelopathy. Additional research is needed to determine the potential efficacy of serotonergic therapy for more common epilepsies with diverse etiologies.

## Serotonin dysfunction may contribute to SUDEP

Premature mortality is significantly greater in epilepsy than the age-matched general population, with standard mortality rates for young adult epilepsy patients estimated to be 6.4 to 8.5 based on a recent systematic review sponsored by the International League Against Epilepsy(35). Annual mortality for pharmaco-resistant epilepsy may be as high as 1–1.5%(36, 37). Studies have consistently found SUDEP to be the most common cause of death in epilepsy, and SUDEP is approximately 25-fold higher in people with epilepsy compared to the general population(38, 39). Some risk factors for SUDEP have emerged through epidemiological and observational studies, such as 3 generalized tonic-clonic seizures (GTCS) per year and lack of caregiver assistance during a seizure, but the specific mechanisms of SUDEP in humans are not known(40). A retrospective analysis of SUDEP events in epilepsy monitoring units found that all cases followed a secondarily GTCS leading to apnea within three minutes postictally and preceding asystole(41). Although available data are not sufficient to determine whether postictal respiratory dysfunction is central or obstructive, respiration has been found to be altered in clinical and animal models of epilepsy. Furthermore, respiratory dysfunction during seizures has been associated with serotonin abnormalities and may be prevented by serotonergic medications.

Although the definitive causes of SUDEP are not yet known, a recent extensive review highlights the potential roles of serotonin dysregulation(42). In addition to the evidence for serotonin depletion or antagonism prolonging or worsening seizures in animal models of epilepsy, serotonin also regulates arousal and respiratory drive. Maximal Electroshock (MES)-induced seizures in mice often result in terminal apnea that precedes asystole for which death can be prevented by mechanical ventilation(43). DBA/1 and DBA/2 mice display respiratory arrest and death following audiogenic seizures; respiratory arrest in this epilepsy model can be prevented by mechanical respiration and by serotonergic augmentation with fenfluramine or optogenetic activation of serotonin neurons in the dorsal raphe nucleus(19, 44).

Multiple studies in humans have informed our understanding of seizure effects of breathing. Oxygen saturation below 90% occurs in one third of focal and generalized seizures(45). Postconvulsive central apnea is observed in 22% of patients with focal and generalized epilepsies, and may be a biomarker for near-SUDEP and SUDEP(46). Higher interictal serum serotonin levels are associated with shorter duration of postictal EEG suppression, and a greater increase in interictal to ictal serotonin level is associated with a shorter tonic phase of tonic-clonic seizures(47). In a subsequent study a greater change in interictal to postictal serotonin was associated with less apneas, further supporting that serotonin may have a protective effect on seizure-related respiratory events associated with SUDEP(48). Lack of permeability of the blood brain barrier (BB) to serotonin may challenge these observations, but epilepsy and seizures have been associated with BBB dysfunction.

Oxygen desaturation of <85% was found to be significantly less in focal seizures in patients taking SSRIs during video/EEG monitoring, but not in secondarily GTCS(49). Analysis of 476 seizures in 204 patients from nine epilepsy monitoring units found that patients with

chronic use of SSRIs had half the risk of ictal central apnea and less oxygen desaturation compared to controls not using SSRIs or benzodiazepines(50).

Altered arousal regulated by serotonin has also been implicated as a possible mechanism for SUDEP. Hypercapnia-induced arousal is an important response for normal sleep homeostasis(51, 52). Mice with marked reduction in serotonin neurons do not arouse with hypercapnic challenges, but do with hypoxic, auditory, and tactile stimuli(53, 54). Furthermore, some data indicate that the “vigilance state” may be protective against SUDEP. For example, MES seizures in mice during REM sleep are universally fatal(55). The additional observation that serotonin neuronal activity is maximal during wakefulness, reduced during NREM sleep, and nearly absent during REM sleep is consistent with nocturnal seizures being a risk factor for SUDEP(56). Some authors have suggested that serotonin system dysfunction with altered arousal, sleep, and postictal obstructive apnea in the prone position may be a particularly lethal combination that explains many cases of SUDEP(42).

### **Serotonin may modulate depression in epilepsy**

Depression and epilepsy are considered to have a bidirectional relationship based on increased risk of occurrence and severity of one in the presence of the other(57–59). The prevalence of depression is higher in epilepsy than other chronic disabling illnesses, suggesting a neurobiological influence(60). Depression precedes the first seizure at higher rates than controls, possibly indicating a common pathogenic mechanism(61, 62). These clinical observations are supported by a rat model bred for depressive behaviors that also develop increased seizure susceptibility(63).

Animal models of the comorbidity of epilepsy and depression have found evidence for multiple potential mechanisms that include most neurotransmitter systems(64). Although multiple etiologies probably contribute to the comorbidity, clinical and animal research support that serotonergic therapies can benefit comorbid depression and epilepsy. The pilocarpine-induced status epilepticus model of spontaneous seizures results in depressive behaviors including increased immobility on the forced swim test (FST) and decreased saccharin ingestion(65). These behaviors are associated with decreased hippocampal serotonin concentrations, turnover, and release. Compounds that produced antidepressant and anticonvulsant effects in this pilocarpine model, including citalopram, imipramine, and fluoxetine, also increased hippocampal serotonin release(66). It is noteworthy that SSRIs such as fluoxetine may not consistently improve depressive behaviors in the pilocarpine seizure model, and may be more effective in combination with a norepinephrine reuptake inhibitor(65, 67). Despite the complexity of the potential mechanisms underlying depression and epilepsy, a recent authoritative review concluded that compromised serotonin transmission was the probable common final pathway and is “the most immediately relevant neurotransmitter system” to understand their comorbidity(68). Human imaging studies of depression in epilepsy using serotonin ligands have identified abnormalities in limbic regions such as the hippocampus, insula, and cingulate gyrus, providing further support for involvement of serotonergic system dysfunction(69–72).

An early trial of depression treatment in epilepsy found no difference between antidepressants and placebo, concluding that “in patients with depression and epilepsy, immediate prescription with antidepressants may not be indicated(73).” Based largely on single case reports, concern emerged about the induction of seizures by SSRIs(74). Subsequent studies supported the safety of SSRIs related to seizure occurrence, including in epilepsy patients(75, 76). Several small studies of depressed epilepsy patients further supported safety and efficacy for SSRIs(77, 78). A recent larger randomized comparative effectiveness trial found that over one half of depressed patients with active epilepsy achieved remission after treatment with either sertraline or cognitive behavior therapy (CBT)(79). The trial was powered to detect a clinically relevant increase in GTCS, and found that sertraline was not associated with increased seizures or suicidality compared to CBT. Consistent with the bidirectional relationship, patients that achieved remission from depression had a significant reduction in GTCS compared to continued depression.

## Conclusion

Serotonin regulates complex neuronal networks involved in seizure susceptibility, breathing and arousal mechanisms possibly contributing to SUDEP, and comorbid depression, as summarized in the schematic in figure 2. Animal models of epilepsy consistently indicate that serotonergic drugs inhibit seizures, but the clinical efficacy in humans is less robust except for some specific epilepsies such as Dravet syndrome. Animal models of SUDEP demonstrate less respiratory arrest and mortality with serotonergic interventions, and human studies indicate that higher serum serotonin concentration and SSRIs are associated with less central apnea and oxygen desaturation. Animal and human studies of SSRIs for the comorbidity of depression and epilepsy indicate efficacy for mood and behavior improvement, safety for seizures and suicidality, and possibly reduction of GTC seizures during remission from depression.

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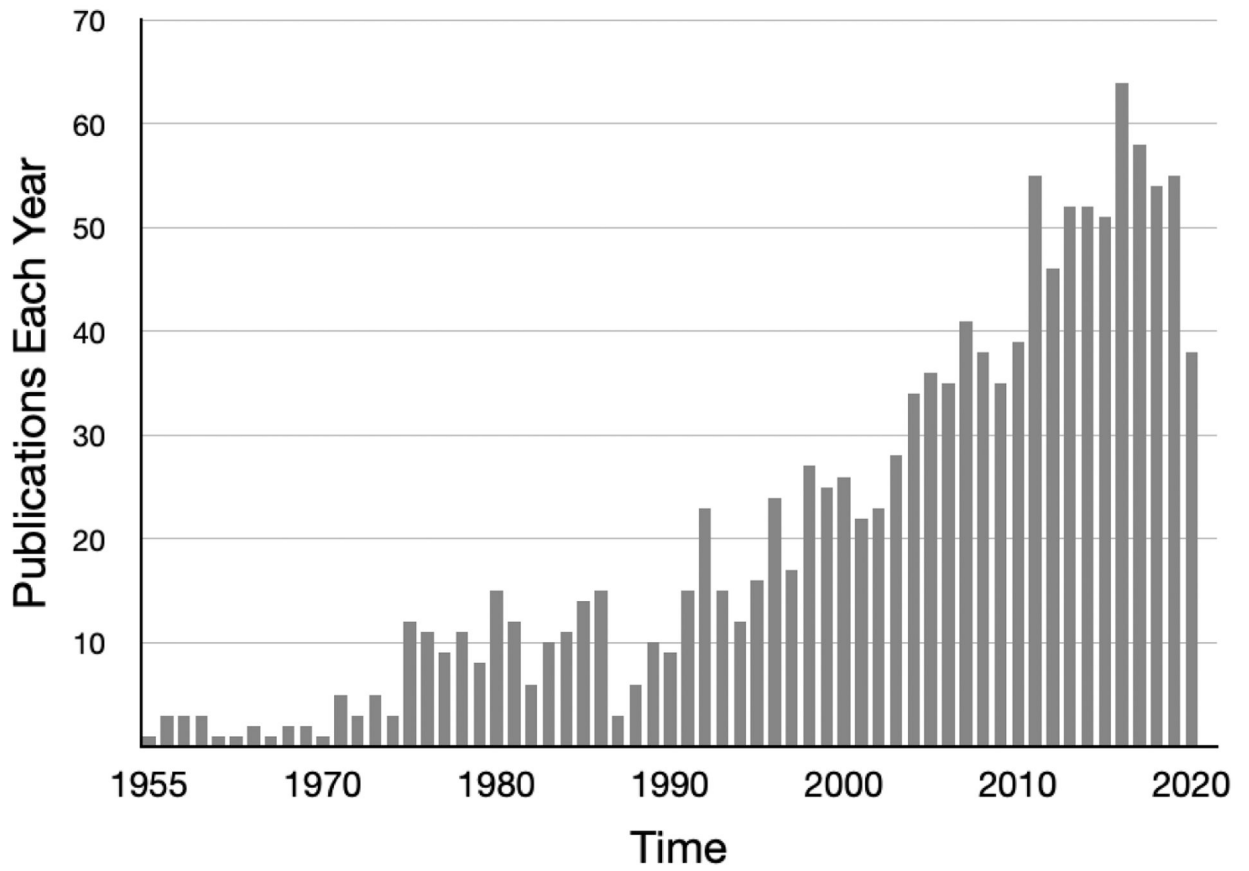
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### Key points

- Although the effects of serotonin on neurons are complex, the net influence appears to be inhibitory for most brain networks.
- Animal models have consistently shown that augmentation of brain serotonin protects against seizures.
- Serotonin agonists and reuptake transporter inhibitors prevent seizures in animal models of the sodium channel defect disease Dravet syndrome, and a randomized, blinded trial of children with Dravet syndrome demonstrated a marked reduction in motor seizures with fenfluramine compared to placebo.
- Ictal central respiratory suppression is a possible cause of SUDEP and may be regulated by brainstem serotonin; selective serotonin reuptake inhibitors (SSRIs) appear to protect against periictal hypoxia.
- Depression is common in epilepsy and serotonin may mediate their bidirectional relationship; despite frequent dysfunction of serotonin networks in epilepsy, SSRIs are effective and safe for depression, and seizures may improve after depression remission.



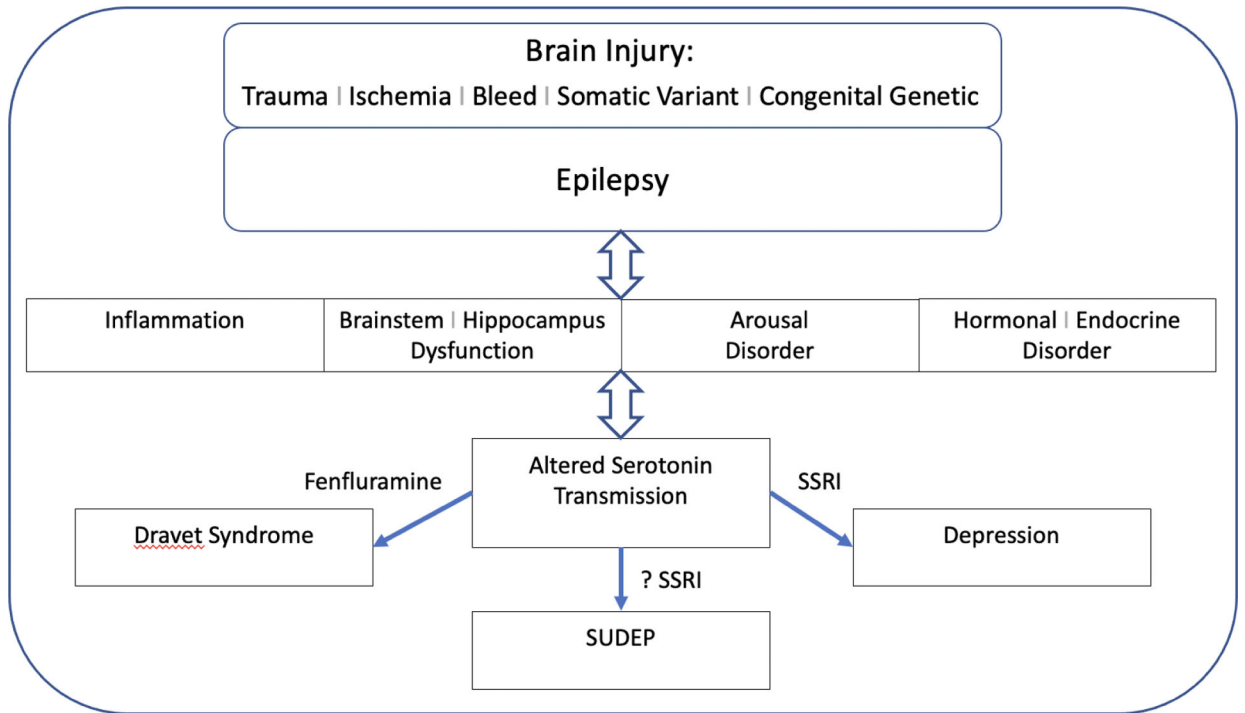
**Figure 1.** Results of [PumMed.gov](https://pubmed.ncbi.nlm.nih.gov/) Search for Serotonin and Epilepsy.

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**Figure 2.** Schematic of brain injury, epilepsy, associated disorders and subsequent altered serotonin transmission resulting in depression, worsened seizures, and possibly SUDEP.

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