Received: 20 August 2021 | Revised: 8 January 2022 | Accepted: 20 January 2022

DOI: 10.1002/epi4.12580

Epilepsia Open® Open Access

CRITICAL REVIEW

Serotonin receptors in epilepsy: Novel treatment targets?

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Abstract

Despite the availability of over 30 antiseizure medications (ASMs), there is no "one size fits it all," so there is a continuing search for novel ASMs. There are divergent data demonstrating that modulation of distinct serotonin (5-hydroxytryptamine, 5-HT) receptors subtypes could be beneficial in the treatment of epilepsy and its comorbidities, whereas only a few ASM, such as fenfluramine (FA), act via 5-HT. There are 14 different 5-HT receptor subtypes, and most epilepsy studies focus on one or a few of these subtypes, using different animal models and different ligands. We reviewed the available evidence of each 5-HT receptor subtype using MEDLINE up to July 2021. Our search included medical subject heading (MeSH) and free terms of each "5-HT subtype" separately and its relation to "epilepsy or seizures." Most research underlines the antiseizure activity of 5-$HT_{1A,1D,2A,2C,3}$ agonism and 5-HT_6 antagonism. Consistently, FA, which has recently been approved for the treatment of seizures in Dravet syndrome, is an agonist of 5-$HT_{1D,2A,2C}$ receptors. Even though each study focused on a distinct seizure/epilepsy type and generalization of different findings could lead to false interpretations, we believe that the available preclinical and clinical studies emphasize the role of serotonergic modulation, especially stimulation, as a promising avenue in epilepsy treatment.

KEYWORDS

5-HT, antiseizure medication, epilepsy treatment, fenfluramine, SUDEP

1 | INTRODUCTION

Epilepsy is a prevalent neurological disease, affecting up to 70 million people worldwide. The ultimate goal for patients with epilepsy (PWE) is to achieve complete seizure control without drug-induced adverse events and preserve the quality of life. The mainstay of epilepsy treatment is controlling seizures by antiseizure medications (ASMs; previously referred to as anti-epileptic drugs, AEDs) that can act through different pathways, that is, an increase of neuronal inhibition and/or a decrease of neuronal excitation.[1]

The first-generation ASMs mainly act by blocking sodium channels or stimulating the neurotransmission by γ-aminobutyric acid (GABA),[2] while second- and third-generation ASMs have distinct molecular targets.[3] Moreover, the pharmacokinetic profile of the newer ASMs has improved, which led to more predictable dose–response effects, fewer side effects, and fewer/no drug–drug interactions.[4] Nonetheless, more than 30% of the

PWE seizures cannot be controlled with the currently available ASMs.[5]

In general, ASM discovery and development are encouraged for orphan diseases (ie affecting <5/10 000 people in the general population), such as Dravet syndrome (DS).[6,7] This strategy has led to the discovery of fenfluramine (FA), a serotonergic drug, that successfully reduces seizures in DS patients.[8] This serotonergic drug is also under evaluation for other severe epilepsy syndromes, such as Lennox–Gastaut and Sunflower syndrome.[9-11] Since preliminary data with this serotonergic drug are promising, it is expected that serotonergic modulation is a promising target to stop (drug-resistant) seizures. Even though FA is believed to affect non-serotonergic pathways as well, such as sigma-1 (σ1) receptors,[12–14] the exact antiepileptic mechanisms are still elusive and it seems likely that serotonin is involved based on preclinical data.[13,15–17]

With this in mind, other studies have underlined that serotonergic receptors seem to be an interesting target for future ASMs.[2,18,19] In addition, ample preclinical and clinical evidence is available to suggest the importance of serotonergic neurotransmission in epilepsy, depression, headache, and sudden unexplained death in epilepsy patients (SUDEP).[18,20,–29] Most compelling evidence of the 14 different serotonin receptors and its role in epilepsy have been reviewed by Gharedaghi and colleagues in 2014.[18]

Therefore, we aimed to update this review with the available research of the last 7 years and provide a comprehensive overview of the modulation of each serotonin receptor in the pathology/treatment of epilepsy.

Key points

- Over 30 antiseizure medications (ASMs) are available, yet one-third of epilepsy patients do not achieve appropriate seizure control.
- Hence, there is an unmet need for ASMs with innovative mechanisms of action, such as serotonergic (5-HT) modulation.
- Until now only one ASM acts via 5-HT, that is, fenfluramine (FA), which likely is a 5-$HT_{1D,2A,2C}$ agonist and approved for Dravet syndrome.
- Interestingly, numerous studies show that 5-$HT_{1A,1D,2A,2C,3}$ agonists and 5-HT_6 antagonists are promising candidates for epilepsy treatment.
- Although generalizing these studies could lead to false interpretations, 5-HT modulation withholds a novel avenue in epilepsy treatment.

2 | MATERIALS AND METHODS

We reviewed the existing literature by means of MEDLINE (using PubMed) up to July 2021, following the PRISMA guidelines (Table S1). The following search with medical subject heading (MeSH) and free terms was used: ((((((((((((5-HT1A receptor) OR (5-HT1A receptor[MeSH Terms])) AND ((((epilepsy) OR (epilepsy[MeSH Terms])) OR (seizures)) OR (seizures[MeSH Terms]))) OR (((5-HT1B receptor[MeSH Terms]) OR (5-HT1B receptor)) AND ((((epilepsy) OR (epilepsy[MeSH Terms])) OR (seizures)) OR (seizures[MeSH Terms])))) OR (((5-HT1D receptor) OR (5-HT1D receptor[MeSH Terms])) AND ((((epilepsy) OR (epilepsy[MeSH Terms])) OR (seizures)) OR (seizures[MeSH Terms])))) OR (((5-HT1E receptor) OR (5-HT1E receptor[MeSH Terms])) AND ((((epilepsy) OR (epilepsy[MeSH Terms])) OR (seizures)) OR (seizures[MeSH Terms])))) OR (((5-HT1F receptor) OR (5-HT1F receptor[MeSH Terms])) AND ((((epilepsy) OR (epilepsy[MeSH Terms])) OR (seizures)) OR (seizures[MeSH Terms])))) OR (((5-HT2A receptor) OR (5-HT2A receptor[MeSH Terms])) AND ((((epilepsy) OR (epilepsy[MeSH Terms])) OR (seizures)) OR (seizures[MeSH Terms])))) OR (((5-HT2B receptor) OR (5-HT2B receptor[MeSH Terms])) AND ((((epilepsy) OR (epilepsy[MeSH Terms])) OR (seizures)) OR (seizures[MeSH Terms])))) OR (((5-HT3 receptor) OR (5-HT3 receptor[MeSH Terms])) AND ((((epilepsy) OR (epilepsy[MeSHTerms]))OR(seizures))OR(seizures[MeSH Terms]))))OR(((5-HT4receptor)OR(5-HT4receptor[MeSH Terms])) AND ((((epilepsy) OR (epilepsy[MeSH Terms])) OR (seizures)) OR (seizures[MeSH Terms])))) OR (((5-HT5 receptor) OR (5-HT5 receptor[MeSH Terms])) AND ((((epilepsy) OR (epilepsy[MeSH Terms])) OR (seizures)) OR (seizures[MeSH Terms])))) OR (((5-HT6 receptor) OR (5-HT6 receptor[MeSH Terms])) AND ((((epilepsy) OR (epilepsy[MeSH Terms])) OR (seizures)) OR (seizures[MeSH Terms])))) OR (((5-HT7 receptor) OR (5-HT7 receptor[MeSH Terms])) AND ((((epilepsy) OR (epilepsy[MeSH Terms])) OR (seizures)) OR (seizures[MeSH Terms]))).

A review of the full text of the obtained articles was performed to exclude articles: (1) without the notion of the role of the 5-hydroxytryptamine (5-HT) receptor subtype in epilepsy and/or seizures and (2) studies that consisted of insufficient data to evaluate one or more 5-HT receptor subtypes in epilepsy and/or seizures. Outcomes of interest were no, proconvulsive or anticonvulsive effects of modulating a distinct 5-HT receptor subtype. In addition, other neurological features by stimulating or blocking the 5-HT receptor subtypes were documented.

Our search has led to 229 publications during the last 20 years, of which 93 elaborated on the effects of distinct 5-HT ligands and epilepsy/seizure treatment. Due to subsequent analyses of these publications' references, 81 other valuable articles were identified. Finally, this led to the inclusion of 174 articles about 5-HT and seven articles about epilepsy and ASM (n = 181 total) (Figure S1: Citation flowchart of search strategy)."

3 | RESULTS

3.1 | 5-HT receptors and epilepsy

Our search has led to 229 publications during the last twenty years, of which 93 elaborated on the effects of distinct 5-HT ligands and epilepsy/seizure treatment. Due to subsequent analyses of these publications' references, 61 other valuable articles were identified. Finally, this led to the inclusion of 154 articles about 5-HT and seven articles about epilepsy and ASM (n = 161 total).

Current research highlights the potential of modulating serotonergic transmission and targeting distinct serotonin (5-HT) receptors in the treatment of epilepsy.[20,30] Consistently, 5-HT is involved in different types of epilepsy, both in a preclinical and clinical setting.[31] This monoaminergic neurotransmitter, 5-HT, affects numerous processes in the human body. During the late 1940s, 5-HT was discovered in the blood causing vasoconstriction of blood vessels.[32] Soon thereafter, its presence was confirmed also in blood vessel walls, blood platelets, enterochromaffin cells, the lungs, and the heart. Even though the majority of 5-HT is present in the gastrointestinal tract (90%, enterochromaffin cells), it is a key player in maintaining normal brain physiology. Hence, it is not surprising that defects in serotonergic transmission have been related to numerous neurological diseases, such as epilepsy and depression.[20,33–35]

5-HT-related research has exploded since the discovery in 1940-1950 resulting in successful approaches to characterize the different 5-HT receptor subtypes. Already by 1980; 5-$HT_{1\text{-like}}$, 5-HT_2, and 5-HT_3 were characterized. However, the classification has changed in the following years due to better insights into molecular biology and secondary pathways. For example, 5-HT_{1C} receptors are now referred to as 5-HT_{2C} sine they have 78% sequence homology with 5-HT_2 receptors. This receptor subtype is coupled to a phosphoinositol (PI) pathway, like the other two 5-HT_2 receptors (5-HT_{2A} and 5-HT_{2B}). Nowadays, receptor classification is based on similarities regarding structural (nucleotide and amino acid components), transduction (secondary pathways), and ligand-binding profiles (drug-related). Overall, 14 5-HT receptor subtypes have been identified and are currently categorized into seven families (5-HT_1-5-HT_7).[36] All 5-HT receptor subtypes are G-protein coupled receptors (GPCR), except the 5-HT_3 subtype. This latter receptor is a ligand-gated sodium-potassium channel, which causes depolarization of the cell membrane, that is, an excitatory effect. The other receptors are GPCR, that is, seven-transmembrane receptors that activate intracellular second messenger cascades. Members of the 5-HT_1 family (5-$HT_{1A,1B,1D,1E,1F}$) and 5-HT_5 decrease adenylyl cyclase (AC) and subsequently cyclic adenosine monophosphate (cAMP) in the cell, causing inhibitory effects. The 5-HT_2 family (5-$HT_{2A,2B,2C}$) increases intracellular concentrations of inositol triphosphate (IP3) and diacylglycerol (DAG) by phospholipase C (PLC) activation, inducing excitation. The following subtype receptors increase AC: 5-HT_4, 5-HT_6, and 5-HT_7, and thus causing excitation as well.[36] There is evidence that targeting different 5-HT receptors and/or affecting 5-HT metabolism and transport could be efficacious in the treatment of epilepsy and its comorbidities (eg, depression).[20,21,31,33,37,38] In 2014, Gharedaghi and colleagues showed that stimulating 5-HT_1, 5-HT_2, or 5-HT_3 receptor subtypes produce anticonvulsive effects. Regarding inhibition of the 5-HT_4-, 5-HT_6-, or 5-HT_7 receptors, the debate is still ongoing and more data are needed regarding the pro- or anticonvulsive effects of the 5-HT_5 receptor.[18,22,31] In addition, various studies have used different compounds that are not always highly selective, different animal models, administration routes, and doses.[18,39] Moreover, controversial and sometimes contradictory findings were published. Thus, all these data should be interpreted with caution and require further research to determine which specific 5-HT ligand(s) could be effective in treating a certain form of epilepsy/epilepsy syndrome or other (neurological) diseases (Table 1).

3.1.1 | 5-HT_{1A} receptors

5-HT_{1A} receptors are the most widely studied receptors in the 5-HT research. Structurally, they differ significantly from the other 5-HT receptors and show similarities to adrenergic receptors that potentially explain the high affinity of several adrenergic agents (eg, propranolol) to 5-HT_{1A} receptors.

Agonists of the 5-HT_{1A} receptor carry potential anxiolytic, antidepressant, anti-epileptic, cognition-enhancing, and neuroprotective effects.[40–43] Currently, several 5-HT_{1A} agonists are used in the clinic for the treatment of anxiety and depression, such as tandospirone and buspirone.[44] Moreover, several researchers suggest the involvement in addiction, alcoholism, behavior, impulsivity, and in the different phases of sleep.[36,45]

TABLE 1 Serotonin (5-HT) receptor modulation and their preclinical/clinical potential

Improvement of (neurological) diseases and/or health features by					
	Stimulation		Inhibition		Main reference(s)
5-HT receptor	Preclinical	Clinical	Preclinical	Clinical	
1A	Aggression, anxiety, craving, depression, epilepsy, impulsivity, sleep	TLE (?), anxiety, depression	Absence epilepsy, cognition	Depression	43,172
1B	Aggression, locomotor activity, sleep	—	—	—	58,172
1D	Depression, epilepsy	Migraine	—	—	59,172
1E	—	—	—	—	64
1F	Migraine	—	—	—	68
2A	Appetite, the absence epilepsy thermoregulation, sleep, SUDEP	Cognition	—	Psychosis, sleep	70
2B	—	—	Cardiotoxicity, schizophrenia, drug addiction	Pulmonary hypertension	94
2C	Appetite, (absence) epilepsy	Appetite, epilepsy	—	—	83
3	Epilepsy, SUDEP	—	Anxiety, cognition, depression, migraine, pain	Nausea, vomiting, psychosis	173
4	Cognition, depression epilepsy, SUDEP	Constipation, IBS, reflux	Anxiety, epilepsy		117
5	Cognition	—	—	—	120
6	Depression	—	Cognition, depression, epilepsy	TLE (?)	121
7	Behavior, cognition, epilepsy, mood	—	Cognition, depression, epilepsy	—	128

Note: (?) indicates uncertain effects of pharmacological modulation of this receptor subtype. See text for all the references of these (pre)clinical studies.

Abbreviations: IBS, irritable bowel syndrome; OCD, obsessive-compulsive behavior; sudden unexplained death in epilepsy patients (SUDEP); TLE, temporal lobe epilepsy.

Regarding epilepsy, some evidence shows that inhibition of the 5-HT_{1A} receptor is anticonvulsive in animal models of the absence epilepsy. For example, several 5-HT_{1A} antagonists reduced spike-wave discharges in Wistar Albino Glaxo/Rijswijk (WAG/Rij) rats and in Groggy (GRY) rats, two validated genetic strains of the absence epilepsy.[31]

In contrast, pharmacological 5-HT_{1A} stimulation could be involved in the anti-epileptic mechanism of several known and novel compounds, such as 8-OH-DPAT,[46] pyrrolidin-2-one derivatives,[47] cannabidiol (CBD),[48,49] and curcumin.[50] Also, endogenous substances, such as hormones, can interact with 5-HT_{1A} receptors as suggested by the cross-talk between estrogenic and serotonergic (5-HT_{1A} and 5-HT_3) pathways.[51] Finally, it could increase the seizure threshold in other seizure types as reviewed by Gharedaghi and colleagues.[18] In addition, 5-HT_{1A} activation can be involved in non-pharmacological therapies, such as the preclinically used low-frequency stimulation (LFS) and nervus vagus stimulation (VNS) in the clinical setting. LFS showed inhibitory activity against seizures in amygdala-kindled rats and was counteracted by a selective 5-HT_{1A} antagonist.[52] VNS can enhance tonic forebrain activation of postsynaptically located 5-HT_{1A} receptors,[53] although its role in epilepsy has not been clarified. 5-HT_{1A} receptors can play a role in status epilepticus,,[54] in epileptogenesis,[55] and in patients with temporal lobe epilepsy (TLE) having decreased 5-HT_{1A} receptor availability.[31,56] 5-HT_{1A} gene polymorphisms can also contribute to the psychiatric comorbidities in TLE patients, indicating a potential role of this receptor subtype in TLE.[57]

Thus, current data suggest a beneficial role of 5-HT_{1A} stimulation in most preclinical epilepsy models (except the absence epilepsy) and patients with TLE. Moreover, anxiety-reducing effects have been reported in a patient with Angelman syndrome (AS) by buspirone.[42]

3.1.2 | 5-HT_{1B} and 5-HT_{1D} receptors

Most of the 5-HT_{1B} receptors are located postsynaptically, although some of them are presynaptically where they are involved in the 5-HT release. Similarities to 5-HT_{1D} receptors for both location and structure have impeded examining the functional role of 5-HT_{1B} receptors and showing overlap with 5-HT_{1D} receptors. Recent studies with newer 5-HT_{1B} ligands, showing high selectivity to 5-HT_{1B} receptors compared to 5-HT_{1D} receptors, suggest a role in behavior, locomotor activity, and sleep regulation.[58] Consistently, 5-HT_{1B} receptor KO mice show aggressive behavior and locomotor impairments. Of interest, these KO mice did not show an epileptic phenotype and several 5-HT_{1B} ligands did not affect seizure activity in animal models. Overall, no straightforward data demonstrate an anticonvulsant role of 5-HT_{1B} agonists in epilepsy.[36]

5-HT_{1D} receptors show a wide distribution throughout the CNS and preclinical research suggests a role in anxiety, depression, and brain disorders (like migraine and Huntington's disease).[36,59] Whereas 5-HT_{1D} agonists are potentially antidepressants more research is needed to determine whether agonists or antagonists could be efficacious in other brain disorders.[36]

Only a few studies are in favor of 5-$HT_{1B/1D}$ agonism for potential epilepsy treatment. Several studies using the drug-resistant DS zebrafish model showed that 5-HT_{1D} agonists significantly reduced seizures.[13,60,61] Interestingly, triptans that are already on the market for the treatment of migraine, showed locomotor reducing activity in two zebrafish models of chemically induced seizures[62] and a chemically induced seizure mouse model (pentylenetetrazol, PTZ).[61] Last but not least, one of the 5-HT_{1D} agonists used in the zebrafish model and another triptan (zolmitriptan) were also effective in a mice model of DS and even significantly improved survival of these mice.[63] The aforementioned data underline the possibility of ameliorating drug-resistant seizures and increasing survival in DS by 5-HT_{1D} agonism. Overall, further research is needed to investigate the potential role of 5-$HT_{1B/1D}$ agonism in the treatment of epilepsy and potential some of its comorbidities such as migraine.

3.1.3 | 5-HT_{1E} and 5-HT_{1F} receptors

As members of the 5-HT_1 family, these receptors are negatively coupled to AC, although the coupling to AC can be achieved by distinct pathways for the 5-HT_{1E} receptor, determined by the density and cellular environment of the receptors. Structurally, the 5-HT_{1F} receptor is most closely related to the 5-HT_{1E} receptor with nearly 60% amino acid homology. In addition, there are several similar pharmacological characteristics.[36,64] Thus, one could expect comparable physiological effects and clinical significance for these two receptor subtypes. Consistently, 5-HT_{1E} and 5-HT_{1F} agonists have been suggested in the treatment of memory impairments,[65,66] though only 5-HT_{1F} agonists are under clinical evaluation for treating migraine.[67–69]

5-HT_{1E} receptors are highly present in the olfactory bulb glomeruli (Table S2), the molecular layer of the dentate gyrus (DG), and the adventitial layer of cerebral arteries. These receptors have a more dominant expression in neurons, compared to glia cells. Agonists of 5-HT_{1E} receptors inhibit AC activity in the DG, thereby modulating hippocampal activity, which makes these agonists a potential drug for the treatment of TLE since hyperactivity in the hippocampus has been linked to TLE.[66]

5-HT_{1F} receptors show a similar expression profile as 5-HT_{1E} receptors. Stimulation of this receptor subtype is assumed to inhibit impulses of the trigeminal nerves, hyperpolarizing nerve terminals. Therefore, 5-HT_{1E} agonists, the "Ditans," are currently being investigated for migraine treatment.[68,69] Nonetheless, we cannot confirm that this receptor subtype would modulate seizures based on the current knowledge.

3.1.4 | 5-HT_2 receptors

A lot has changed since the initial identification of 5-HT_2 receptors. The primarily CNS-located 5-HT_2 receptors were later renamed to 5-HT_{2A} receptors, together with the discovery of the 5-HT_{2B} receptors that are predominantly distributed in the peripheral system. In addition, the 5-HT_{1C} receptors were called 5-HT_{2C} receptors due to similarities in structure and secondary pathways, for example, PLC activation.[36] In the past decades, numerous selective agents have been developed that are able to discriminate between these three subpopulations, resultantly making it possible to examine their distinct clinical significance.[70] In vitro data show that augmented serotonin increases cortical excitation through activation of 5-HT_2 and 5-HT_3 receptors,[71] suggesting that antagonism of these receptors would induce anti-epileptic effects. Clinical data underline the potential of 5-HT_2 and 5-HT_3 antagonism, by mirtazapine, in the treatment of sleep disturbances in patients with AS.[72] As delineated below, subtypes of the 5-HT_2 receptors (5-HT_{2A}, -$_{2B}$, and -$_{2C}$) can play a crucial role in current and future epilepsy treatment.

In essence, compelling preclinical and clinical evidence indicates that 5-$HT_{2A/2C}$ stimulation leads to antiseizure activity and could ameliorate epilepsy-related comorbidities, for example, depression and SUDEP. In clear contrast, only one zebrafish research group suggested the anticonvulsive role of 5-HT_{2B} stimulation.[73] In addition, the prominent expression of this receptor subtype in the heart[74] and related cardiotoxic effects[75–78] underscore that the 5-HT_{2B} subtype is not an interesting target for epilepsy treatment.[21,79]

3.1.5 | 5-HT_{2A} receptors and 5-HT_{2C} receptors

These receptors are present in the brain and the highest densities are found in the neocortex. As described for the 5-HT_{1E} receptor, two pathways can be activated depending on the location and cellular environment of the 5-HT_{2A} receptor.[36] These distinct pathways can explain the hallucinogenic properties of some 5-HT_{2A} agonists (mainly activating arachidonic acid pathways, eg, LSD) and the absence of hallucinations by other 5-HT_{2A} agonists (mainly affecting phosphoinositide signaling, eg, lisuride).[80,81] Structurally, the 5-HT_{2A} receptor is very closely related to the 5-HT_{2C} receptor with almost 80% homology in the transmembrane (TM) portions, possibly explaining some binding overlap of ligands for both receptor subtypes. As a consequence, many clinical effects can involve both 5-HT_{2A} and 5-HT_{2C} receptors; such as appetite control, thermoregulation, locomotor activity, and sleep. In addition, several researchers suggested these receptors to be promising targets for antidepressants, antipsychotics, and definitely antiepileptic drugs.[33,36,78,82–84] A review by Guiard and Di Giovanni thoroughly describes the controversial role of 5-HT_{2A} receptors in epilepsy wherein proconvulsant properties are likely to be attributed to the use of high doses of 5-HT_{2A} ligands and/or off-target effects by modulating other receptors. Of interest, FA is not only increasing 5-HT in the synaptic cleft (indirect) but also directly targeting 5-HT_{2A} (and 5-HT_{2C}) receptors.[76]

Regarding the absence epilepsy, stimulation of the 5-HT_{2A} and/or 5-HT_{2C} receptor could be beneficial since it inhibits the rhythmic thalamic burst firings which are likely to be the electrical burst origin of the absence epilepsy. Consistently, several 5-HT_{2A} agonists show promise in treating atypical the absence seizures and 5-HT_{2A} antagonists increase the severity of seizures[21,85] and diminished the anti-epileptic effect of FA in several preclinical models.[15,16]

Furthermore, the 5-HT_{2A} receptor regulates mood[33] and modulates CO_2-induced arousal and stimulation of this receptor subtype can rescue animals from SUDEP.[29,86,87] These findings underline that 5-HT_{2A} agonists can decrease epilepsy and ameliorate its comorbidities such as depression and SUDEP.

The 5-HT_{2C} receptor is likely to be involved in the epileptiform activity as well since 5-HT_{2C} KO mice display an epileptic phenotype and 5-HT_{2C} antagonists worsen the seizure phenotype[88,89] and can counteract the anti-epileptiform activity of FA.[13] Additionally, 5-HT_{2C} agonists are anticonvulsive in models of atypical absences,[21] acute seizure models,[83,84] drug-resistant seizures in the zebrafish model of DS,[13,28] and have been used in human studies to treat drug-resistant epilepsy.[90,91] Nonetheless, there are few studies that demonstrate no antiseizure effects by 5-HT_{2A} and/or 5-HT_{2C} agonism.[18] Moreover, overstimulation of these receptors can be proconvulsive[92] and 5-HT_{2A} antagonism showed antiseizure effects in one rodent epilepsy model.[93] In addition, 5-HT_{2A} antagonism had a positive effect on short-term memory, which possibly expands the role of modulating this receptor subtype in other diseases, beyond epilepsy.[18]

3.1.6 | 5-HT_{2B} receptors

Even as 5-HT_{2B} receptors exhibit almost 70% homology to the other two 5-HT_2 receptor subtypes, their expression profile is nearly absent in the brain and appears to be mainly involved in vasoconstrictive effects in the vascular and cardiac system.[74,75,77] Hence, it is not surprising that only scanty data are available regarding the role of 5-HT_{2B} receptors in neurological disorders.

Recent rodent data indicate that 5-HT_{2B} antagonists hold promise for treating schizophrenia and drug addiction, due to the interaction of 5-HT_{2B} and dopamine.[94] Additionally, three studies suggest the role of 5-HT_{2B} in epilepsy treatment. First, in a PTZ-kindling rat model of chronic epilepsy increased immunoreactivity of the 5-HT_{2B} receptor was found in the cortex and medulla, while it was decreased in the hippocampus. However, further behavioral/functional studies are necessary to elucidate the meaning of this immunoreactivity alteration.[95] Second, the novel ASM, CBD, reduced seizures in pilocarpine-induced SE in rats that was attributed to both CB_1 and 5-HT_{2B} receptors,[96] although 5-HT_{2B} receptors are probably not involved in CBD's mechanism of action as shown by Dos Santos et al[48] and Pelz et al[97] Third, Baraban et al showed that 5-HT_{2B} agonists can reduce seizures in the zebrafish DS model. Nonetheless, numerous other researchers did not observe any seizure reduction by 5-HT_{2B} modulation in different animal models of epilepsy.[18,29,63,84,89,90,98–106] For example, Sourbron et al did not demonstrate any beneficial effect of several 5-HT_{2B} agonists in the aforementioned zebrafish DS model[13,28] and 5-HT_{2B} antagonism was not able to counteract the anti-epileptiform activities of the serotonergic drug, FA, in this DS model.[13] Therefore, FA is unlikely to be anti-epileptic through 5-HT_{2B} agonism. Nevertheless, the *N*-dealkylated metabolite of FA, norfenfluramine (NORFA), displays higher affinity and activity at the 5-HT_{2B} and 5-HT_{2C} receptors. This activation of 5-HT_{2B} receptors is associated with cardiac valve hypertrophy, and the drug-induced valvulopathy has resulted in the withdrawal of FA from the market in the 1990s.[107] Even though drug-induced valvulopathy could lead to pulmonary hypertension (PH), clinical trials with lower dose FA monitor cardiac side effects and until now its safety has been guaranteed.[108] In contrast, 5-HT_{2B} antagonists are a potential novel therapeutic target for treating PH, for example, terguride, a potent 5-HT_{2B} antagonist, is being investigated as a PH treatment.[109]

3.1.7 | 5-HT_3 receptors

5-HT_3 receptors are expressed in the peripheral nervous system but also in the CNS. From a clinical perspective, 5-HT_3 antagonists have shown efficacy in treating nausea and vomiting, if induced by chemotherapy or radiation but not if it is triggered by motion sickness or apomorphine.[36] Moreover, clinical data demonstrate its use in migraine treatment and preclinical studies showed a potential of 5-HT_3 ligands in anxiety, cognition, depression, dementia, memory enhancement, and psychosis. The effect on seizures is in ongoing debate and some authors suggest that this receptor is not involved. Most preclinical data are in favor of 5-HT_3 stimulation to suppress seizures[18,110]; for example, 5-HT_3 antagonists increase the frequency of hippocampal theta bursts, which is related to generalized tonic-clonic seizures and eliminated the anticonvulsive properties of 5-HT_3 agonists.[111,112] In addition, 5-HT_3 agonism blocked seizure-induced respiratory arrest in a mouse model of SUDEP[100] and alleviated acute seizure activity[103] and in PTZ-kindling in mice.[113] Even as the 5-HT_3 receptor is an excitatory receptor it is mainly located on inhibitory interneurons (in cortex and hippocampus) leading to hyperpolarisation and thus less excitation in the brain, comparable to the 5-$HT_{2A/2C}$ receptors.[21] Nevertheless, it can cause NO production by activation of neuronal nitrite oxide synthase, which is potentially proconvulsive in several seizure models.[114] This could explain that the 5-HT_3 antagonism decreases seizures in PTZ-kindled mice[102] and that ondansetron, a 5-HT_3 antagonist is anticonvulsant in the MES test.[18,22] Lamotrigine, an ASM already available on the market, acts on sodium and calcium channels but also inhibits 5-HT_3-activated currents.[115] Until now, it is unknown if this latter pathway is involved in its anti-epileptic activity.

Altogether, most data attribute an anticonvulsive role to 5-HT_3 stimulation, especially in models for generalized seizures, for example, acute PTZ and PTZ kindling murine models.[31,103] Recent data even show that the anticonvulsant effect of various SSRIs involves 5-HT_3 stimulation.[113] In conclusion, 5-HT_3 agonists could be interesting in ASM development although side effects can be anticipated due to stimulation of the chemoreceptor trigger zone that can cause bradycardia, nausea, and vomiting.[31]

3.1.8 | 5-HT_4 receptors

5-HT_4 receptors have an extended tissue distribution and play a role in the slow excitatory responses to 5-HT in neurons. Structurally, there is some overlap between 5-HT_4 and 5-HT_3 ligands. Currently, research is focused on both central and peripheral effects of 5-HT_4 ligands in diseases, such as addiction, anxiety, cognition, irritable bowel syndrome, and gastroesophageal reflux.[36,116,117] Available data are very limited in the epilepsy field, although the

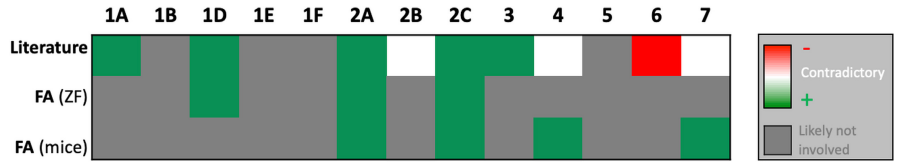

FIGURE 1 Fourteen serotonin (5-HT) receptor subtypes. Stimulation (+) of several receptor subtypes (5-$HT_{1A,1D,2A,2C,3}$) and inhibition (−) of the 5-HT_6 subtype have been implicated in antiseizure activity (row literature). For the 5-$HT_{2B,4,7}$ subtypes data are contradictory, depicted in white. 5-$HT_{1D,2A,2C}$ subtypes are likely involved in the mechanism of fenfluramine (zebrafish (ZF) data). 5-$HT_{2A,2C,4,7}$ subtypes are likely involved in the mechanism of fenfluramine (mice data). See text for the references of these preclinical studies

majority is in favor of 5-HT_4 antagonists as potential anticonvulsant treatment. These compounds nullified epileptiform spikes, induced by 5-HT_4 agonists, and reduced forelimb clonus in amygdala-kindled rats.[18] In contrast, 5-HT_4 stimulation increases GABA inhibitory currents in the hippocampal dentate gyrus of guinea pigs,[118] 5-HT_4 KO mice experience more aggravated PTZ-induced seizures, compared to WT mice,[119] and recent data show that FA prevented SUDEP and reduced seizures by 5-HT_4 receptor stimulation, although 5-HT_2 and 5-HT_7 receptors could be involved as well.[16] In conclusion, data are contradictory and future preclinical studies should elaborate on the exact role of 5-HT_4 receptors in different seizure models.

3.1.9 | 5-HT_5 receptors

5-HT_5 receptors are structurally unrelated to other 5-HT receptor subtypes, however, they share some pharmacological properties with 5-HT_{1D} receptors. Not much is known about the clinical significance but based on their localization (cortex, astrocytes); suggestions have been made regarding anxiety, brain development, cognition, depression, feeding, and locomotor activity.[120] It is currently not known if these receptors are involved in epileptogenesis and/or epilepsy.[18,31]

3.1.10 | 5-HT_6 receptors

The clinical significance of the 5-HT_6 receptors subtype is currently unknown but it appears to be involved in several neuropsychiatric processes (depression, psychosis, and obsessive-compulsive behavior) and recent evidence underlined a procognitive role of both 5-HT_6 agonists and antagonists.[121] Even though data regarding the role of this receptor subtype in epilepsy are very limited, the beneficial effects of highly selective 5-HT_6 antagonists are relatively more robust in animal models of seizures[122–124] and mossy fiber sprouting,[125] in contrast to 5-HT_6 agonists. Spontaneous seizures in the post-SE pilocarpine rat model were reduced after treatment with a highly selective 5-HT_6 antagonist. In addition, 5-HT_6 receptor expression was upregulated in the hippocampus and neocortex of these post-SE rats.[31,105,126] In line with these findings, clinical data of patients with drug-resistant TLE show an upregulation of this receptor as well.[105] Thus, current data favor a proconvulsive role of the 5-HT_6 receptor.

3.1.11 | 5-HT_7 receptors

Due to the wide distribution of 5-HT_7 receptors in the CNS, it is not surprising that it can be involved in several neurological processes and pathophysiology. Structurally, there is less than 50% TM sequence homology between this and the other 5-HT receptor subtypes. This receptor affects cognitive processes, mood, circadian rhythm, and the relaxation of coronary arteries. Consequently, 5-HT_7 ligands could be effective in treating memory impairments, behavioral dysfunction, sleep disorders of circadian nature, and coronary heart disease.[127,128] Regarding epilepsy, most researchers are in favor of a proconvulsive role of the 5-HT_7 receptor. For example, numerous 5-HT_7 antagonists were proven to be anticonvulsant in different animal models of seizures like the pilocarpine rat model of TLE, WAG/Rij rats, and the DBA/2 J mice model of the absence epilepsy.[18,129] This latter finding could be attributed to the fact that the thalamus, considered to be the origin of electrical discharges in the absence epilepsy is enriched with 5-HT_7 binding sites. However, 5-HT_7 agonism decreased seizures in mice picrotoxin-induced seizure[130] and partially rescued the brain anomalies and epileptic phenotype in *Cdkl5* KO mice.[131] In addition, 5-HT_7 KO mice have decreased seizure thresholds for electrical and chemical-induced seizures.[132]

Overall, several experimental data are in favor of a proconvulsive role of the 5-HT_7 receptor, in line with patient data with drug-resistant TLE that have an upregulated expression of 5-HT_7 receptors in the neocortex,[106] although the exact role is not uniform.[133]

3.2 | 5-HT system and epilepsy, comorbidities and mortality

Involvement of the 5-HT system in epilepsy, comorbidities, and mortality has been suggested by several researchers[20,21,22,23,26,27,30,38,134] (Figure 1) and until now FA is potentially the only ASM modulating the 5-HT system (Figure 2). The importance of shared risk factors and especially genetics appear to be key players.[134] Some even hypothesize that the cause could directly be related to 5-HT system impairments. For instance, a patient with a de novo mutation in the sodium voltage-gated channel alpha subunit (*SCN2A*) had drug-resistant epilepsy that responded to treatment with the 5-HT precursor, 5- hydroxytryptophan (5-HTP).[135] In addition, decreased hippocampal 5-HT levels were observed in patients with TLE.[136] Preclinical evidence is even more prominent showing, for example, that 5-HTP was anticonvulsant in drosophila with an *SCN1A* mutation.[137] In addition, a zebrafish model of DS (*scn1a* mutation) demonstrated a lower 5-HT brain content that could be related to the *scn1a* mutation.[60]

For numerous epilepsy-associated problems, the 5-HT system seems to be involved and reduced 5-HT transmission seems to negatively impact several epilepsy comorbidities, such as motor functions,[138] behavior,[139] depression, migraine, and cognitive impairments.[140] Regarding depression, a plethora of evidence underlines the antidepressant activity of 5-HT and effective depression therapy with SSRIs.[38] Interestingly, a relation between epilepsy and depression was linked to 5-HT_{1A}[141,142] and 5-HT_{2A}[33] receptors.

With regards to migraine, experimental and patient evidence exists regarding the efficacy of agonists for the 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors. More recent yet limited data demonstrate anti-migraine activities for 5-HT_{2B} and 5-HT_7 antagonists in animal models of migraine.[143] The link between 5-HT and cognition has been extensively studied and 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_4, 5-HT_6, and 5-HT_7 ligands show preclinical and clinical efficacy in treating cognitive defects. Nevertheless, these data are limited and focus on the older population and patients with AD and schizophrenia. Moreover, controversial findings impede making a general conclusion toward the potential of certain 5-HT agonists or antagonists in treating cognitive defects.[144]

SUDEP applies to death in PWE that is not related to known causes like injury and drowning. Studies imply that the overall risk for SUDEP is greater than 0.1% in the general epilepsy population although estimates vary significantly.[145] Moreover, SUDEP is one of the most severe consequences for patients with drug-resistant epilepsy and SUDEP appears to be the major cause of death in patients with drug-resistant DS.[146,147] Currently, the exact mechanisms SUDEP are unknown

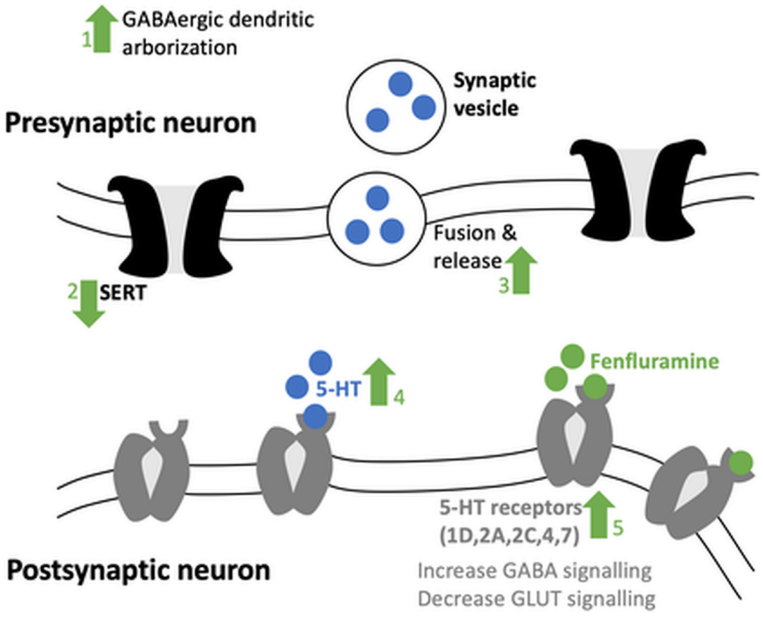

FIGURE 2 Serotonergic mechanisms of action of fenfluramine: (1) increase of GABAergic dendritic arborization via 5-HT and GABAergic activity[168]; (2) decrease of serotonin reuptake by inhibition of SERT[169]; (3) increase of fusion and release of synaptic vesicles[170]; (4) the two previous modulatory lead to an increase of 5-HT in the synaptic cleft and thereby stimulation of 5-HT receptor subtypes; and (5) fenfluramine directly stimulates at least five serotonin (5-HT) receptor subtypes (5-$HT_{1D,2A,2C,4,7}$) (zebrafish and mice data),[13,171] thereby increasing gamma-aminobutyric acid inhibitory input and decreasing glutaminergic excitatory output. Regarding the sigma receptor modulation, we refer to Martin et al 2020.[12] 5-HT = serotonin; GABA = gamma aminobutyric acid; GLUT = glutamine; SERT = serotonin transporter

and the majority of research points out that SUDEP can be the result of respiratory dysfunction that is immediately followed by a seizure.[148,149] Several experimental studies suggest the importance of 5-HT in SUDEP. For example, 5-HT_{2C} KO mice have spontaneous seizures and earlier mortality due to respiratory arrest, compared to WT mice.[89] In addition *Lmx1b* KO, mice lacking the development of serotonergic neurons, have a relatively higher seizure threshold and higher chance to die from respiratory failure that was prevented by stimulating 5-HT_{2A} receptors.[29] Moreover, human studies have shown that many PWE can have hypoxia after a seizure,[150] which can be reduced by taking SSRIs, increasing 5-HT in the synaptic cleft.[151] The overall importance of 5-HT in SUDEP can be related to the 5-HT-dependent regulation of breathing and sleep arousal to keep normal blood CO_2 and pH values.[152] Recently, Cross and colleagues showed that the all-cause and SUDEP mortality rates during FA treatment of patients with DS significantly decreased (1.7/1000 person-years), compared to literature reports (9.3-15.8/1000 person-years).[153]

3.3 | 5-HT system and cardiovascular side effects

Serotonergic drugs that directly or indirectly lead to 5-HT_{2B} receptor activation are indeed associated with cardiac valve hypertrophy. Stimulation of 5-HT_{2B} receptors, which are GPCR (Table S2), leads to activation of PLC that subsequently activates protein kinase C (PKC). PKC mobilizes intracellular calcium and DAG. Via other, yet to be explored, pathways this GPCR can also induce Src phosphorylation and activation of extracellular regulated kinases (ERK1/2). Moreover, phosphorylated Src modulates the transforming growth factor β (TGF-β) receptor, enhancing the 5-HT_{2B}-stimulated mitogenesis that involves the phosphorylation of retinoblastoma protein (Rb-P). Moreover, the PKC and ERK1/2 similarly modulate Rb-P leading to excessive mitogenesis, thereby causing overgrowth valvulopathy and valvular dysfunction. Hence, drugs that stimulate the 5-HT_{2B} receptor could induce cardiac valvulopathies.[76,154,155]

Fenfluramine was initially used as an anti-obesity drug but was withdrawn from the market due to drug-induced valvulopathy that was related to abuse, use of other amphetamine-like drugs and/or high doses.[75] Even though several preclinical data show that 5-HT_{2B} stimulation is not mandatory for a seizure reduction by FA, FA can increase 5-HT and thereby indirectly stimulate 5-HT_{2B} receptors. Fortunately, much lower dosages are used in the clinic and clinical trials nowadays[156,157] and after more than 3 years of treatment with low-dose FA, no cardiotoxic events have been observed.[158] These data, together with the durability and magnitude of FA's reduction of drug-resistant seizures,[159] strongly suggest that significant benefits of FA could outweigh potential cardiac risks. Regarding other, possibly serotonergic side effects, clinical trials mainly report decreased appetite (potential role of 5-HT_{2C}) and somnolence (5-$HT_{?}$).[160–162]

4 | CONCLUSION

Antiseizure medication development has been focusing on neurotransmitters and ion channels involved in excitatory and inhibitory neurotransmission.[163] In the last decade, research implies that the complex variety of pathways involved in epilepsy, such as serotonergic (5-HT) transmission, are neglected by this simplistic view. Nonetheless, the exact role of each serotonin (5-HT) receptor subtype remains elusive, in part due to contradictory findings.[18,31]

Our review underlines that most evidence is in favor of 5-$HT_{1A,1D,2A,2C,3}$ agonism and 5-HT_6 antagonism to treat epilepsy. Even though the role of the other receptor subtypes is unclear, one should be cautious to generalize these findings and discrepancies might arise due to a number of factors, for example, the difference in animal seizure models and the difference of compounds and their doses.[18,164]

Interestingly, serotonergic ASMs are currently under development for rare, severe epilepsy syndromes and one of them, FA, showed promising results by numerous clinical studies.[9,11,108,165–167] Even as FA likely displays (part of its) anti-epileptic activity via sigma1 (σ1) receptors,[12,14] other zebrafish and mice studies have shown that FA-induced 5-$HT_{1D,2A,2C}$ agonism plays a crucial role in its antiseizure activity[13,15] and even 5-$HT_{4,7}$ agonism has been suggested by one study.[17] Serotonergic agonism of 5-$HT_{2A,2C,4}$ receptors can also ameliorate epilepsy-related mortality (SUDEP).[16,87]

In conclusion, the available research strongly suggests that serotonergic modulation, especially stimulation, should be a novel avenue for future ASMs to treat epilepsy and its comorbidities.

CONFLICT OF INTEREST

LL received grants, and is a consultant and/or speaker for Zogenix; LivaNova, UCB, Shire, Eisai, Novartis, Takeda/Ovid, NEL, Epihunter. LL has a patent for ZX008 (fenfluramine) for the treatment of Dravet syndrome and infantile epilepsies assigned to his institution and licensed to Zogenix. The remaining author (JS) has no conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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How to cite this article: Sourbron J, Lagae L. Serotonin receptors in epilepsy: Novel treatment targets? Epilepsia Open. 2022;7:231–246. https://doi.org/10.1002/epi4.12580