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Review

Most antidepressant drugs are safe for patients with epilepsy at therapeutic doses: A review of the evidence

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ABSTRACT

For a long time, there has been a misconception that all antidepressant drugs have proconvulsant effects. Yet, antidepressants of the selective serotonin reuptake inhibitor (SSRI) and serotonin–norepinephrine reuptake inhibitor (SNRI) families have been not only shown to be safe when used in patients with epilepsy (PWE) but have been found to display antiepileptic properties in animal models of epilepsy. In humans randomized to SSRIs vs. a placebo for the treatment of primary major depressive episodes, the incidence of epileptic seizures was significantly lower among those treated with the antidepressants. On the other hand, SSRIs and SNRIs can display proconvulsant properties at toxic doses. This article reviews the preclinical and clinical data of antiepileptic and proconvulsant properties of these drugs and addresses special considerations to take when prescribing them for PWE.

1. Introduction

Mood and anxiety disorders are the most frequent psychiatric comorbidities in patients with epilepsy (PWE), with lifetime prevalence rates ranging between 30% and 35% [1]. Accordingly, we would expect that antidepressant drugs would be frequently prescribed for these patients, particularly since most of these drugs can yield a therapeutic effect in depressive and anxiety disorders. Yet, such is not the case, and one of the reasons stems from a long-standing misconception held by clinicians that antidepressant drugs cause seizures. This false belief constitutes one of the obstacles in the pharmacologic treatment of mood and anxiety disorders in PWE. Furthermore, data from several animal models of epilepsy have suggested that drugs of the serotonin reuptake inhibitor (SSRI) and tricyclic antidepressant (TCA) families may yield an antiepileptic effect [2,3]. The first part of this review summarizes the data on the impact of antidepressant drugs on seizures in experimental studies and in patients with and without epilepsy. In the second part, we highlight special considerations that need to be taken into account when antidepressants are used in PWE.

2. Do antidepressant drugs really have proconvulsant properties?

The "proconvulsant effect" of antidepressant drugs is one of the most misunderstood facts in the practice of medicine, which unfortunately has had dire consequences as it has precluded many physicians from prescribing these psychotropic drugs to PWE. The fact is that, with the exception of four drugs (see below), the reported seizures associated with antidepressants have occurred when taken at very high doses (e.g., in the setting of overdoses) [4,5]. For example, one study revealed that the minimum citalopram dose associated with seizures was 400 mg [6]. In fact, this observation has been supported experimentally in a study of pilocarpine-induced seizures in rats in which hippocampal perfusion of serotonin (5-HT), up to extracellular concentrations above 900% of baseline, worsened seizures. On the other hand, at concentrations ranging from 80% to 350% of baseline levels, 5HT protected these rats from seizures [7].

The inclusion of seizures as an iatrogenic effect of antidepressants (including SSRIs and SNRIs) in the Physician Desk Reference has perpetuated the concern of prescribing these drugs to PWE since this document does not clarify the conditions under which seizures tend to occur. Furthermore, seizures in patients with a primary mood and anxiety disorder may have resulted from an unidentified medical and/or neurologic condition and yes, from the underlying psychiatric disorder. Indeed, in the last two decades, several population-based studies have suggested that mood and anxiety disorders may be a risk factor for the development of epilepsy [8–11]. Interestingly enough, these data support an observation made by Hippocrates twenty-six centuries ago when he wrote "*melancholics ordinarily become epileptics and epileptics melancholics*: *what determines the preference is the direction the malady takes*; *if it bears upon the body*, *epilepsy*, *if upon the intelligence*, *melancholy*" [12]. In other words, these studies suggest the existence of a bidirectional relation between epilepsy and psychiatric disorders whereby not only are PWE at greater risk of developing these psychiatric disorders, but patients with primary mood and anxiety disorders have a two- to seven-fold higher risk of developing epilepsy. This phenomenon

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has also been described in pediatric patients with epilepsy [13]. Thus, the occurrence of a seizure in a depressed or anxious patient who is being treated with an antidepressant drug may be the expression of the natural course of these psychiatric disorders and not of an iatrogenic effect of the psychotropic drug.

The proconvulsant effect of antidepressant drugs was clarified in a pivotal study by Alper et al., who reviewed data from the Food and Drug Administration Phases II and III clinical regulatory trials of several TCAs, SSRIs, the serotonin–norepinephrine reuptake inhibitor (SNRI) venlafaxine, the α2 antagonist mirtazapine, and the norepinephrine–dopamine reuptake inhibitor bupropion in patients with primary depression [14]. These investigators compared the incidence of epileptic seizures between patients randomized to the antidepressant drug and to a placebo, and they found a significantly lower seizure incidence among patients assigned to antidepressants (standardized incidence ratio = 0.48, 95% CI, .36–.61). While the seizure incidence was greater in patients randomized to the drug and the placebo than the published incidence of unprovoked seizures in the general population, the seizure incidence was 19-fold higher among patients randomized to the placebo. These data support the increased risk of depressed patients for the development of unprovoked seizures and epilepsy alluded to above and suggest a protective effect of SSRIs and SNRIs. The two antidepressant drugs associated with a higher incidence of seizures than the placebo included clomipramine and bupropion. Separate reports had made a similar observation with respect to bupropion (0.5%–4.8% in a dose-dependent manner) and clomipramine (1%–12.2% in a dose-dependent manner) and had identified amoxapine and maprotiline (incidence: 15.6% in a dose-dependent manner) as two other antidepressant drugs associated with an increased risk of seizures [3]. In summary, with the exception of these four drugs, antidepressant drugs are safe for PWE when used at therapeutic doses.

3. Do antidepressant drugs have antiepileptic properties?

Antidepressant drugs, in particular SSRIs and SNRIs, have become the first line of treatment of depression and anxiety disorders in patients with and without epilepsy [15]. Furthermore, antiepileptic properties of SSRIs have been suggested in several experimental studies, which are briefly reviewed below.

The primary pharmacodynamic aim of SSRIs and SNRIs is to increase the synaptic concentration of monoamines, in particular 5HT and norepinephrine (NE). Thus, to demonstrate potential antiepileptic properties, it would be necessary to demonstrate the following: (i) a pathogenic role of serotonergic and/or noradrenergic mechanisms in seizure activity, (ii) a role of monoamines in the antiepileptic effects of antiepileptic drugs (AEDs), and (iii) an antiepileptic effect of SSRIs and SNRIs in several animal models of epilepsy and in double-blind randomized placebo-controlled trials of these drugs in PWE. Of these three conditions, no data are yet available on controlled trials of these drugs in PWE.

3.1. Pathogenic role of monoamines in epilepsy

The pathogenic role of 5HT in epilepsy has been suggested in functional neuroimaging studies using positron emission tomography (PET) in PWE and in experimental animal models of epilepsy.

3.1.1. Neuroimaging studies

Five studies with PET using various $5HT_{1A}$ receptor antagonists in patients with temporal lobe epilepsy demonstrated a decrease of $5HT_{1A}$ binding in several neuroanatomical structures including the epileptogenic hippocampus, amygdala, and anterior cingulate and lateral temporal neocortex (ipsilateral to the seizure focus), as well as in the contralateral hippocampus and in the raphe nuclei [16–20]. Furthermore, reduction in $5HT_{1A}$ receptor binding has also been found in generalized epilepsy in the dorsolateral prefrontal cortex, raphe nuclei, and hippocampus of 11 patients with juvenile myoclonic epilepsy compared to 11 controls [21].

3.2. Experimental data

A potential pathogenic role of 5HT in epilepsy has been suggested in several animal models of focal and generalized epilepsy. For example, an abnormal serotonergic axon arborization, associated with deficient postsynaptic $5HT_{1A}$ receptor density, has been demonstrated in the hippocampus of genetically epilepsy-prone rats (GEPRs) [22], an animal model of generalized epilepsy in which generalized tonic–clonic seizures are induced with audiogenic stimuli. Furthermore, elevation of 5HT levels with the SSRIs fluoxetine, citalopram, and sertraline resulted in a dose-dependent seizure frequency reduction, which correlated with the extracellular serotonergic thalamic concentration [23], while the 5-HT precursor 5-hydroxytriptophan (5-HTP) has been shown to have anticonvulsant effects when combined with a monoamine oxidase inhibitor (MAOI) [24].

The pathogenic role of 5HT in animal models of focal epilepsy has also been suggested in a model of status epilepticus in male Wistar rats, in which Mazarati et al. demonstrated a decrease of hippocampal 5-HT concentration and turnover as well as a lower 5-HT release from the hippocampus in response to raphe nuclei stimulation [25]. Prendiville et al. demonstrated that fluoxetine prevented seizures when preadministered in the bicuculline (a GABA antagonist) model of focal epilepsy in rats [26], while 5HT agonists have been found to block seizures in other models of focal epilepsy [27].

4. Does 5HT mediate the antiepileptic effect of AEDs?

An increase in extracellular 5HT has been found in the GEPR after the administration of several first and second generation AEDs, including phenytoin, carbamazepine, valproic acid, lamotrigine, oxcarbazepine, and zonisamide [24,28–37]. For example, after establishing an anticonvulsant effect of carbamazepine in the GEPR, Yan et al. showed that the addition of 5HT-depleting drugs results in a blockage of this anticonvulsant protection [24]. Likewise, Clinckers et al. investigated the impact of oxcarbazepine (OXC) infusion on the extracellular hippocampal concentration of 5HT and DA in the focal pilocarpine model for limbic seizures [31]. When oxcarbazepine was administered together with verapamil or probenecid (to ensure its passage through the blood–brain barrier), complete seizure remission was obtained, associated with an increase in 5HT and DA extracellular concentrations [32]. Furthermore, SSRIs such as fluoxetine enhance the anticonvulsant effects of phenytoin, carbamazepine, phenobarbital, and valproate in the maximal electroshock seizure model in mice [30].

The antiepileptic effect of $5HT_{1A}$ receptors has been associated with a membrane hyperpolarizing response associated with increased potassium conductance in hippocampal-kindled seizures in cats and in intrahippocampal KA-induced seizures in freely moving rats [38,39]. A recent study has also suggested that the SSRI sertraline could markedly reduce the increase of proinflammatory cytokine expression induced by seizures and convulsant agents and by the inoculation of lipopolysaccharide in the hippocampus including IL-1β and TNF-α mRNA expression [40].

The pharmacologic effect of SSRIs influences other neurotransmitter systems involved in epileptogenesis and seizure propagation such as cholinergic neurons in the septum and glutamatergic neurons in the hippocampus and forebrain regions, where 5HT agonists stimulate acetylcholine and inhibit glutamate release, respectively [41]. Furthermore, stimulation of $5HT_{1A}$ receptors in thalamic relay neurons results in an increase in GABA release and, consequently, a decrease in excitatory activity necessary for spike–wave discharges in absence seizure models [41]. A review by Hamid and Kanner provides a more in-depth discussion of experimental data suggesting an antiepileptic effect of SSRIs [2].

4.1. Clinical trials

To date, only open trials of SSRIs and SNRIs in PWE have been published [42–45]. All were descriptive and suggested that these drugs had no negative impact on seizure frequency. Two trials suggested a reduction in seizure frequency, but these studies were not powered to show antiepileptic efficacy and were not controlled. Thus, an antiepileptic effect of these drugs is yet to be established in PWE.

4.2. Special considerations on the use of antidepressants in PWE

Depressive and anxiety symptoms may be the expression of an underlying interictal disorder, they may represent postictal symptoms, or they may have resulted from an iatrogenic effect of introduction and/or discontinuation of AEDs. Therefore, before starting any pharmacologic treatment with a psychotropic drug, the following causes of psychiatric symptoms must be excluded: (1) administration of AEDs with negative psychotropic properties (e.g., barbiturates, benzodiazepines, topiramate, levetiracetam, zonisamide, vigabatrin, tiagabine, and perampanel); (2) discontinuation of AEDs with anxiolytic (e.g., pregabalin and gabapentin) and/or mood-stabilizing properties (e.g., valproic acid, carbamazepine, oxcarbazepine, and lamotrigine) that were keeping an underlying anxiety/depressive disorder in remission; and (3) the target symptoms are preictal, ictal, or postictal symptoms, as these symptoms do not respond to pharmacotherapy with antidepressants [46–48].

The aim of any type of pharmacologic treatment must be geared towards complete symptom remission, as persistence of symptoms, even in the presence of improvement, is associated with a significant risk of recurrence of a major depressive episode (MDE). Furthermore, antidepressant drugs should not be started in patients with a bipolar disorder, unless they are taking a mood-stabilizing agent, as antidepressants can facilitate the development of manic and hypomanic episodes or of a rapid cycling bipolar disorder (i.e., four or more depressive, manic, or hypomanic episodes in a 12-month period) [49].

As stated above, the first line of treatment of depressive and anxiety disorders in patients with and without epilepsy includes the use of SSRIs or SNRIs. The choice of the specific SSRIs and/or SNRIs depends on the following variables: 1) type of depressive episode (SNRIs are preferred for retarded depressive episodes, e.g., fatigue and slow thinking; otherwise, patients should be started on an SSRI); 2) therapeutic profile in depressive and anxiety disorders, given their high comorbidity in PWE; 3) potential pharmacokinetic and pharmacodynamic interactions with concurrent AEDs; and 4) potential adverse event profile of the specific SSRI drug that could worsen underlying medical complications associated with the seizure disorder or other concurrent medical conditions (i.e., obesity and sexual disturbances). Failure to reach remission of symptoms following a trial with an SSRI at optimal doses should be followed by a switch to an SNRI and vice versa.

Patients should be started at a low dose and with stepwise increments until achieving a symptom-free state, developing adverse events, or reaching the maximal dose, whichever occurs first. Table 1 summarizes the starting and maximal doses of SSRIs and SNRIs, their efficacy in mood and anxiety disorders, and whether they are subject to pharmacokinetic interactions with AEDs.

Furthermore, SSRIs and SNRIs can be associated with relatively frequent adverse events, which require close supervision, and patients should be advised to alert the clinician upon their occurrence. These include the following: gastrointestinal symptoms (nausea and diarrhea with prevalence rates of 35% and 19%, respectively), headaches in 15%, insomnia in 25%, dry mouth in 13%, and sexual disturbances in 10 to 20% [50]. In addition, osteoporosis and osteopenia have been associated with these drugs, but the actual prevalence is yet to be established. In addition, SNRIs can be associated with excessive sweating, hypertension, and a syndrome of inappropriate antidiuretic hormone secretion leading to hyponatremia, a potential adverse event identified in patients taking venlafaxine (but not duloxetine) [51]. Duloxetine should be used with great care in patients with a history of liver disease and should be avoided in those with glaucoma.

4.3. Pharmacokinetic properties of antidepressants and interaction with AEDs

The achievement of the optimal serum concentration of SSRIs and SNRIs may be prevented when used together with first generation AEDs such as phenytoin, carbamazepine, phenobarbital, and primidone and the third generation AED rufinamide, which are inducers of the cytochrome p450 (CYP) enzyme system. Oxcarbazepine and topiramate are much less potent inducers of CYP 3A4. Indeed, the majority of antidepressant drugs are substrates for one or more of the CYP isoenzymes, and comedication with any of these AEDs would be expected to increase their systemic clearance, specifically, that of sertraline, paroxetine, citalopram, and escitalopram [52]. Accordingly, their dose must be increased by 30% in order to ensure an optimal therapeutic antidepressant response [52,53]. In contrast to the enzyme-inducing drugs, the AED sodium valproate can inhibit certain CYP (2C9) and UDP-glucuronosyltransferase enzymes, but no interaction with SSRIs or SNRIs has been reported.

By the same token, antidepressants of the SSRI family can inhibit several CYP isoenzymes [53–55,46–48] with the exception of citalopram and escitalopram, while sertraline has mild inhibitory effects. Fluoxetine has been shown to inhibit CYP 3A4, CYP 2C9, CYP 2C19, CYP 2D6, and CYP 1A2. Its metabolite, norfluoxetine, has also been shown to inhibit CYP 2D6, while fluvoxamine is an inhibitor of CYP 1A2, CYP 3A4, CYP 2C9, and CYP 2C19. Inhibition of CYP 3A4, CYP 2C9, and CYP 2C19 is of the most relevance when considering potential effects on the currently available AEDs, leading to increased phenytoin and carbamazepine serum concentrations [52,53,54]. Although definitive studies are lacking, it has also been suggested that venlafaxine and duloxetine are unlikely to cause significant interactions with currently available AEDs [52,53].

Less clinical data are available regarding pharmacokinetic interactions between antidepressants and the newer generation AEDs. Given that the newer AEDs are in general less reliant upon the CYP isoenzyme

Table 1
Efficacy and doses of SSRIs and SNRIs in primary depression and anxiety disorders.

Antidepressant drug	Depression	Panic disorder	Generalized anxiety	Starting dose	Maximal dose	Inhibits some AEDs	Clearance increased by EIAED
Paroxetine[a]	+	+	+	10	60	Yes	Yes
Sertraline[a]	+	+	+	25	200	Mild	Yes
Fluoxetine[a]	+	+	−	10	80	Yes	?
Citalopram[a]	+	+	+	10	60	No	Yes
Escitalopram[a]	+	+	+	5	30	No	No
Fluvoxamine[a]	+	+	+	50	300	Yes	No
Venlafaxine[b]	+	+	+	37.5	300	No	No
Duloxetine[b]	+	+	+	20	120	No	No

+: used for the treatment of this condition. +: has FDA indication for this condition.
[a] SSRI.
[b] SNRI.

system for their disposition, it is likely that there will be fewer opportunities for pharmacokinetic interactions.

4.4. Pharmacodynamic interactions between AEDs and antidepressants

One of the concerns that clinicians have to always keep in mind is the potential worsening of adverse events resulting from the combination of antidepressant drugs and AEDs that have common adverse events. Yet, the observations of this section are theoretical with limited data. From a theoretical standpoint, the following potential synergistic adverse events have to be looked for carefully:

(1) Potentiation of weight gain that can be caused by AEDs such as gabapentin, valproic acid, carbamazepine, pregabalin, and the SSRIs and SNRIs.
(2) Potentiation of sexual adverse events: Sexual adverse events, such as decreased libido, anorgasmia, and sexual impotence can be relatively common with AEDs such as the barbiturates (phenobarbital and primidone) but can also be seen with other enzyme-inducing AEDs, related to the synthesis of sex-hormone-binding globulin, which binds the free fraction of sex hormones and hence limits their access to the CNS. As mentioned above, SSRIs and SNRIs are known to cause sexual adverse events. Whether the combination of this types of AEDs and antidepressants has a "synergistic adverse effect" on sexual functions has yet to be established. The direct impact of the seizure disorder on sexual functions is an additional confounding variable which could, in fact, be the variable responsible for the decreased sexual drive independently of the exposure to the AEDs and/or antidepressant drugs.
(3) Potentiation of osteopenia and osteoporosis between enzyme-inducing AEDs and SSRIs: Several population-based studies have suggested that exposure to SSRIs is associated with decreased bone mineral density (BMD) and bone fractures (level IIb). For example, one study found higher rates of bone loss at the hip for SSRI users, even after controlling for possible confounders like depression [55]. In a Canadian population study, the adjusted odds ratio for hip fracture was 2.4 (95% CI, 2.0–2.7) for exposure to SSRIs compared to nonusers [56]. A third population-based study carried out in the Netherlands found the risk of nonvertebral fracture to be 2.35 (95% CI, 1.32–4.18) for current users of SSRIs compared with nonusers of antidepressants, after adjustment for age, sex, lower-limb disability, and depression [57]. The pathogenic mechanisms by which SSRIs may cause osteopenia have been attributed in preclinical studies to the serotonin transporter (which has been demonstrated in human osteoclasts, osteoblasts, and osteocytes). Investigators have found that bone mineral accrual was impaired in growing mice treated with an SSRI [58]. Clearly, these data raise the question of whether the use of SSRIs increases the risk of osteopenia and osteoporosis, which has been recognized for a long time with enzyme-inducing AEDs.
(4) Serum sodium must be monitored when SNRIs are used together with carbamazepine, oxcarbazepine, and eslicarbazepine.
(5) Excessive sweating may also be associated with lamotrigine, and sexual dysfunction can worsen a pre-existent disturbance associated with the seizure disorder or an iatrogenic effect caused by barbiturates.

5. Concluding remarks

Antidepressant drugs of the SSRI and SNRI families are safe for PWE and should be used at therapeutic doses for the management of depressive and anxiety disorders. Antidepressants can cause seizures at toxic doses, and only four drugs have revealed proconvulsant effects at therapeutic doses: clomipramine, bupropion, amoxapine, and maprotiline. Clearly, these drugs should be used with great caution in PWE.

Conflict of interest

I have no conflict of interest to disclose.

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