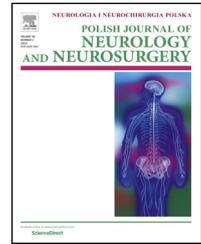


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## Review article

## Antidepressants in epilepsy

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## ABSTRACT

People with epilepsy (PWE) frequently suffer from comorbid mood and anxiety disorders. Depression is one of the major psychiatric comorbidities having a negative impact on the quality of life in people with epilepsy. A review of the literature indicates that the majority of antidepressant-related seizures have been associated with either ultra-high doses or overdosing and, generally, the risk of antidepressant-associated seizures is low. Correspondingly, there is some evidence indicating that antidepressants of most widely used groups may additionally lower the risk of triggering seizures. Four antidepressants are not recommended for patients with epilepsy, i.e.: amoxapine, bupropion, clomipramine and maprotiline. Clinicians applying first line of depression treatment in patients with epilepsy should consider use of SSRIs or SNRIs, particularly sertraline, citalopram, mirtazapine, reboxetine, paroxetine, fluoxetine, escitalopram, fluvoxamine, venlafaxine, duloxetine. Implementation of anticonvulsive drugs in depressed patients should include valproate, carbamazepine, lamotrigine, gabapentin, pregabalin. The paper reviews the evidence for the clinical use of antidepressants in PWE.

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## 1. Introduction

People with epilepsy (PWE) frequently suffer from comorbid mood disorders. Lifetime prevalence ranges between 11% and 62% [1]. One of the major psychiatric comorbidities having a negative impact on the quality of life in PWE is depression [2]. The relationship between depression and epilepsy may be bidirectional; having depression would increase the risk of epilepsy, and having epilepsy appears to increase the risk of depression [3]. Suicide attempts among depressed PWE are four- to fivefold more frequent than in the general population [4–6]. Depression has also been associated with higher rates of

drug resistance in PWE [7]. Considering these issues the successful and safe treatment of depression associated with epilepsy is of utmost clinical importance.

Also psychotherapy must be mentioned as effective and safe therapeutic intervention in PWE suffering from depression [8].

Guidelines indicating the choice of psychotropic drugs in PWE are mainly based on studies in patients without epilepsy, as well as risk evaluation of seizures [9,10].

Antidepressants may impact the incidence of seizures in a dose-related manner in line with the animal model of epilepsy [11]. The anticonvulsive effect is noticed at low doses and with the increase of the dose the effect is

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being reversed [12]. A review of the literature indicates that most antidepressant-related seizures have been associated with either ultrahigh doses or particularly in overdosing [13].

The paper reviews best practice indications for antidepressant treatment in patients with epilepsy.

## 2. Antidepressants – the impact on the occurrence of seizures

People with epilepsy or with familial history of epilepsy, the ones suffering from other neurological disorders, patients with pre-treatment electroencephalographic (EEG) abnormalities, cerebral arteriosclerosis, those suffering from other general medical conditions like hypertensive encephalopathy and the elderly ones are more likely to experience seizures related to antidepressants [11].

First-generation antidepressants, particularly tricyclic antidepressants (TCAs) exhibit capacity to trigger seizures in patients without epilepsy [14].

Amoxapine, bupropion, clomipramine and maprotiline may trigger convulsions even if administered at the therapeutic dose range [15]. Imipramine dosed up to 200 mg per day was associated with the increased seizure risk: from 0.1% to 0.6–0.9% at higher doses [16].

Retrospective observational study has demonstrated that selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs) worsened seizure frequency, but also may be associated with a possible decrease in seizure frequency. This data revealed a drop-in seizure frequency from  $\geq 1$  to below 1 seizure for month in 27.5% of patients with frequent seizures, non-relevant to change in psychiatric symptoms, what may suggest that SSRIs potentially yield a positive anticonvulsive effect in patients with treatment-resistant epilepsy [17].

No influence of citalopram, mirtazapine and reboxetine on the incidence of seizures was noticed in a 30-weeks study in patients with temporal epilepsy and major depression [18].

Data from FDA Phases II and III clinical regulatory trials of several TCAs, SSRIs, SNRI – venlafaxine, noradrenergic and specific serotonergic antidepressant (NaSSA) – mirtazapine, and the norepinephrine–dopamine reuptake inhibitor (NDRI) – bupropion in patients with major depression, indicate that the incidence of seizures was significantly lower among patients assigned to antidepressants than to placebo [19]. Therefore, the occurrence of a seizure in a depressed patient who is being treated with an antidepressant drug may be the expression of the natural course of psychiatric disorder and not of an iatrogenic effect of the psychotropic drug [20].

## 3. ADT – mechanism of action and the incidence of seizures

There are three main elements, which caused a creation of psychopathology in epilepsy [21]: those related to the brain, as in this case, factors with neurobiological characteristics shared by depression and epilepsy [22], those related to treatment, i.e. depressogenic anticonvulsants, such as tiaga-

bine, vigabatrin, topiramate, and phenobarbital [23] and those unrelated to the brain, such as stigma and social discrimination or patients' use of maladaptive strategies (e.g., non-acceptance of the disease) [24]. Kanner and Palac [25] agree with this concept, stating that a combination of intrinsic and extrinsic factors that act synergistically causes depression in epilepsy.

Longer-term adaptations to antidepressants, mediated via second-messenger systems and implicating changes in gene expression and protein translation lead to downstream effects on neurogenesis and other conditions of neuroplasticity, the neuroendocrine system [particularly the hypothalamo–pituitary–adrenal (HPA) axis], other neurotransmitter systems and inflammatory pathways. Much evidence also denotes both neurotrophins, (e.g. BDNF), and epigenetic mechanisms in these manifold actions. These diverse pathways and mechanisms become compelling when aiming to identify the mechanisms by which these compounds may also impact on epilepsy [26]. Astonishing hippocampal neuroplasticity is considered to be a predominant feature of obtained epilepsy and represents a strong candidate mechanism by which antidepressant drugs may impact on disease processes. While HPA axis hyperactivity is one of the most stationary characteristics in depressed patients [27], this system has also been verified to be dysfunctional in epilepsy.

The ability of antidepressants to affect HPA axis regulation and the evidence suggesting a damaging role of glucocorticoids in epilepsy development, promotes the HPA axis as a potential site of interaction whereby antidepressants could influence epileptogenesis and seizure vulnerability. A broad literature circumscribes monoamine anomalies in the pathophysiology of both epilepsy and depression [28]. Since many of the new generation antidepressants point monoaminergic neurotransmission, these systems present nominees to mediate the influence of antidepressants on seizures and epilepsy evolution. Inflammation is another biological process which is significant in the pathogenesis of epilepsy [29], which has also a connection with antidepressants [30].

## 4. Interaction between antidepressant drugs and AEDs

Interactions and potential worsening of adverse events resulting from the combination of antidepressant drugs and antiepileptic drugs (AEDs) are important issue in everyday clinical practice.

Clinicians should carefully look for two domains of potential adverse effects: (1) increased weight gain that can be caused by AEDs such as gabapentin, valproate, carbamazepine, pregabalin, and the SSRIs and SNRIs, (2) sexual dysfunction: 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, limiting their access to central nervous system [20]. Antidepressants can also aggravate sexual dysfunction [31].

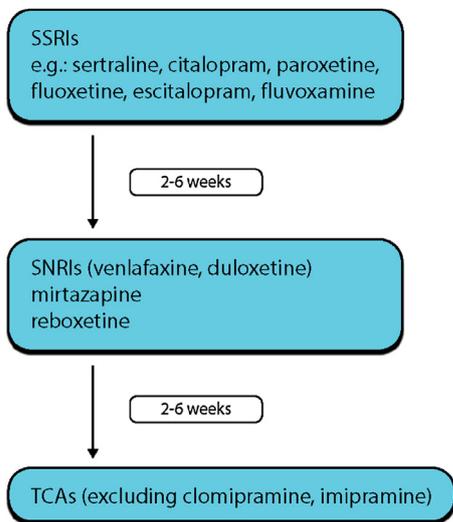


Fig. 1 – Major depression treatment in epilepsy.

Some AEDs (e.g. carbamazepine) have been shown to increase clearance of antidepressants, while some antidepressants can inhibit clearance of AEDs as they interact with the cytochrome P450 hepatic enzyme system [32].

### 5. ADT in epilepsy

The adequate selection of AEDs for particular patients is the key issue – prescribing drugs with negative psychotropic characteristics to patients with a personal or family psychiatric history must be avoided. Moreover, discontinuation of AEDs which have mood-stabilizing properties (e.g. lamotrigine, carbamazepine, valproate and oxcarbazepine) or anxiolytic characteristics (e.g. gabapentin, benzodiaze-

ines or pregabalin) has to be monitored carefully since these drugs may be indicated with regard to mood disorders [15].

Some vital variables must be considered by the choice of the specific SSRIs and/or SNRIs: (1) characteristics of depressive episode (SNRIs are preferred for depressive episodes with fatigue and psychomotoric decline; otherwise, SSRI should be used); (2) therapeutic profile in depressive and anxiety disorders, given their high comorbidity in PWE; (3) possible pharmacodynamic and pharmacokinetic interactions with concomitant AEDs; and (4) potential adverse event profile of the specific SSRI drug that could worsen underlying medical complications merged with the seizure disorder or other attendant medical conditions. The implementation of the therapeutic serum concentration of SSRIs and SNRIs may be prevented by using first generation AEDs such as phenytoin, carbamazepine, phenobarbital, and primidone and the third generation AED rufinamide, which induce the cytochrome P450 enzyme system [33–36].

One of the largest study included 97 patients with epilepsy treated with sertraline. A possible, transient worsening of seizures was observed in 5 patients and only one patient was thought to suffer a clear deterioration in seizure control [37]. Two studies have even found an anticonvulsive effect of citalopram and fluoxetine in epilepsy [38,39]. SSRIs (e.g., citalopram, sertraline, fluoxetine) and SNRIs (e.g., venlafaxine, duloxetine) represent the first-line agents for pharmacological treatment [39–41]. On the other hand, tricyclic or tetracyclic antidepressants and norepinephrine-dopamine reuptake inhibitors (NDRI) should be avoided in the first choice [40]. Noradrenergic and specific serotonergic antidepressants (NaSSAs) appear to be safe in epilepsy as well [41]. Also ketamine has recently been shown as promising antidepressant [42], which actions may be linked to the mTOR pathway [43], a pathway recently been implicated in an ample range of models of epileptogenesis [44].

Table 1 – Antidepressants in PWE. Based on [18,19,50].

Drug	Dosing	Metabolism	Interaction with ASDs	Seizure risk	Level of evidence
SSRIs	Approved therapeutic doses	Liver (CYP450)	Carbamazepine, phenytoin (decrease level of some SSRIs)	Low/no influence	II
SNRIs	Approved therapeutic doses	Liver (CYP450)	Carbamazepine (decreases level of duloxetine)	Low/no influence	II
Mirtazapine	15–45 mg	Liver (demethylation, oxidation, conjugation with proteins)	Topiramate (increase sedation) Carbamazepine, phenytoin (increase metabolism)	Low/no influence	IA
Reboxetine	4–12 mg	Liver (CYP3A4)	Phenytoin, carbamazepine, phenobarbital (decrease level)	Low/no influence	III
Imipramine	30–300 mg	Liver (CYP1A2, CYP3A4, CYP2C19, CYP2D6)	Phenytoin, carbamazepine, phenobarbital, topiramate, (decrease level)	Medium (0.1–0.9%)	III
Bupropion	150–300 mg	Liver (mainly CYP2B6)	Carbamazepine (increases metabolism) Valproate (decreases metabolism)	Medium/high	IA
Amoxapine	200–600 mg	Liver (CYP450)	Carbamazepine (increased metabolism) Topiramate (increased sedation)	High	II
Clomipramine	10–225 mg	Liver (CYP3A4, CYP2C19, CYP1A2)	Phenytoin, carbamazepine, topiramate (decrease level)	High	II
Maprotiline	25–150 mg	Liver (CYP2D6, CYP1A2)	Phenobarbital, topiramate (increase sedation) Carbamazepine (decrease level)	High	III

### 5.1. ADT in temporal lobe epilepsy

Temporal lobe epilepsy (TLE) has a more significant risk of depression than extratemporal epilepsy. Patients with temporal lobe epilepsy commonly afflict major depression with a prevalence rate between 20 and 60% [45–47]. Kühn et al [48] investigated the efficacy and safety of depression treatment with mirtazapine, citalopram and reboxetine in patients with temporal lobe epilepsy.

Cognitive-behavioral therapy (CBT) has a comparable effect as SSRIs for treating MDD in patients with TLE. The main malalignment of SSRIs was that, SSRIs appear to have less influence on patients' quality of life (QOL), when equated to CBT (Table 1) [49].

## 6. Conclusion

In summary, indication for best practice for ADT in PWE is: SSRIs or SNRIs including citalopram, escitalopram, sertraline, fluoxetine, mirtazapine, reboxetine, paroxetine, fluvoxamine, venlafaxine and duloxetine. With the exception of four drugs (amoxapine, bupropion, clomipramine and maprotiline) antidepressant drugs are generally safe for PWE when used at therapeutic doses. The discerning insight into this issue may lead to a supposition, that antidepressant drug-induced convulsions are rather a result of an overdose or slow metabolism which results in high plasma concentrations of antidepressants [51]. Data appear to reaffirm previous observations derived from open trials that SSRIs and SNRIs do not aggravate seizure frequency and therefore should be used for the treatment of comorbid mood disorders in PWE [6,19–21].

## Conflict of interest

Dr. Cubała has received research support from Actavis, Alkermes, Allergan, Auspex, Biogen, Bristol-Myers Squibb, Cephalon, Eli Lilly, Ferrier, Forest Laboratories, Gedeon Richter, GW Pharmaceuticals, Janssen, KCR, Lundbeck, Orion, Otsuka, Sanofi, and Servier; he has served on speakers bureaus for Adamed, Angelini, AstraZeneca, Bristol-Myers Squibb, Celon, GlaxoSmithKline, Janssen, Krka, Lekam, Lundbeck, Novartis, Orion, Pfizer, Polfa Tarchomin, Sanofi, Servier, and Zentiva; and he has served as a consultant for GW Pharmaceuticals, Janssen, KCR, Quintiles, and Roche.

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