The pharmacological management of psychiatric comorbidities in patients with epilepsy

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Abstract

Psychiatric disorders represent a frequent comorbidity in patients with epilepsy affecting quality of life, morbidity and mortality. Evidence-based data on the management of these conditions are limited but a number of recommendations are now available to guide clinical practice. The present paper reviews the pharmacological treatment of psychiatric problems in epilepsy with special attention to data coming from randomised controlled trials (RCTs), pharmacological interactions with AEDs and the issue of seizure worsening during treatment with psychotropic drugs. Epidemiologically or clinically relevant psychiatric conditions are discussed namely mood and anxiety disorders, psychoses and attention deficit hyperactivity disorder.

Key words: epilepsy, depression, anxiety, psychosis, attention deficit hyperactivity disorder, interactions, antiepileptic drugs, antidepressant drugs, antipsychotic drugs, methylphenidate

1. Introduction

Psychiatric disorders represent a frequently reported comorbidity in patients with epilepsy affecting both mortality and morbidity (1). Epidemiological data show a uniformly increased prevalence in epilepsy as compared to the general population (2) and, in some cases, this partially reflects the severity of the seizure disorder as prevalence rates are higher in subjects with refractory syndromes as compared to patients with well controlled epilepsies (3). However, the clinical scenario seems to be more complex than that with multiple variables involved such as psychosocial issues (4), adverse effects of antiepileptic drugs (AEDs) (5) or neurobiological factors directly related to the seizures or the epileptic disorder (6). **Moreover, it is now established that patients with epilepsy may experience a number of behavioural changes or psychiatric symptoms around the ictus that should be differentiated from comorbid psychiatric conditions. Historically, such symptoms have been classified according to their temporal relationship to the occurrence of seizures for practical reasons (peri-ictal/para-ictal symptoms and interictal symptoms) (Table 1). In the past, a number of authors identified and described these symptoms. In particular, Gowers (7) and Jackson (8) but also by Kraepelin (9) and Bleuler (10) pointed out that, in untreated patients, epileptic seizures can be accompained by a number of psychiatric symptoms and behavioural changes.** The differentiation between peri-ictal and interictal psychiatric symptoms has relevant implications in terms of prognosis and treatment as peri-ictal symptoms are due to the underlying seizure disorder and AEDs remains the main treatment.

The present paper reviews the pharmacological treatment of interictal psychiatric conditions with special attention to data coming from randomised controlled trials (RCTs), pharmacological interactions with AEDs and the issue of seizure worsening during treatment with psychotropic drugs. Epidemiologically or clinically relevant psychiatric conditions are discussed namely mood and anxiety disorders, psychoses and attention deficit hyperactivity disorder.

2. MOOD DISORDERS

2.1 Evidence from RCT in epilepsy

Data on treatment of depression in epilepsy is still limited and relies heavily on clinical experience. The only double-blind trial on antidepressants in epilepsy was published 30 years ago and compared nomifensine, amitriptyline and placebo (11). Since then, a number of open trials in small samples of unselected patients with different epilepsy types have been published: sertraline (12,13), citalopram (14–16), reboxetine (15), mirtazapine (15), and fluoxetine (13). One study is of particular interest because it is the only published paper involving children and adolescents with epilepsy and depression (13). All these antidepressants showed to be effective and well tolerated but due to the lack of controlled about the pharmacological treatment of depression in epilepsy, the Epilepsy Foundation (17) and the International League Against Epilepsy (18) published a number of recommendations to guide clinicians. In general terms, it is reasonable to follow internationally accepted guidelines for the treatment of mood disorders outside epilepsy, applying individual adjustments, in the individual patient, according to the epilepsy type and the concomitant AEDs (19).

In general terms, it is important to distinguish between the acute treatment of depression (aimed at remission and recovery) and the long term treatment (aimed at avoiding recurrence). It is also important to point out that the patient is in *remission* when all symptoms go away. If remission lasts for 6 to 12 months, the patient is then considered in *recovery*. Worsening before a remission or before a remission has turned into a recovery, it is called *relapse* while a new episode after complete recovery is defined *recurrence*. Epidemiological studies of depression show that up to 90% of patients respond to one treatment or a combination of therapeutic interventions and among these subjects about 50% recover within 6 months and up to 75% in 2 years (20). It is still unknown whether patients with epilepsy and depression have similar remission and recovery rates although it is reasonable to hypothesise so.

2.2 Pharmacokinetic interactions between antiepileptic and antidepressant drugs

Antidepressants are usually classified into older or classic agents, such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), and newer antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs) and other antidepressants with varying mechanisms of actions (21). A number of papers have reviewed pharmacokinetic interactions between antidepressant and antiepileptic drugs (22,23).

2.2.1 The effect of AEDs on antidepressants

Among first generation of AEDs, carbamazepine (CBZ), phenytoin (PHT) and barbiturates (PB) are powerful inducers of several drug-metabolizing enzymes including CYPs (CYP 1A2, 2A6, 2B6, 2C9, 2C19, 3A4) and UGTs (1A1, 2B7, 2B15). Valproate (VPA) has been traditionally considered a broad spectrum enzyme inhibitor on the CYPs (2C9, 2C19 and 3A4) and UGTs (1A4 and 2B7) (23). As all these enzymes contribute to the metabolism of the majority of antidepressants, these AEDs may present pharmacokinetic interactions with antidepressants.

As far as TCAs are concerned, their metabolism is quite complex with multiple enzymatic pathways involved. Demethylation is mainly catalysed by CYP2C19, and to a lesser extent CYP1A2, 2C9 and 3A4, while hydroxylation is primarily catalysed by CYP2D6 (22,23). Regarding the potential clinical relevance of pharmacokinetic interactions with AEDs, a number of factors have to be considered: (i) nortriptyline and desipramine are the demethylated metabolites of amitriptyline and imipramine, respectively; (ii) TCAs have a large therapeutic window; (iii) CBZ in particular seems to affect also the protein binding leading to a significant increase in the free fraction (24). For all these reasons, it is unlikely that interactions between TCAs and first generation AED inducers are clinically relevant and dosage adjustments may be needed on an individual basis rather than in a systematic way. The same principles apply for VPA. VPA can inhibit several metabolic pathways involved in TCA metabolism but toxic levels have been reported only in some rare cases (25,26). Clinicians should therefore monitor patients and adjust dosages in individual cases rather than adopting systematic dose adjustments.

Regarding SSRIs, first generation inducers (i.e. CBZ, PHT and PB) seem to reduce the plasma levels of the majority of them by at least 25% (23). Again, whether this is clinically relevant depends on the individual patient. Studies on VPA are limited but it seems that there are no clinically relevant pharmacokinetic interactions.

As far as other antidepressants are concerned, inducers like CBZ, PHT or barbiturates obviously reduce the plasma levels of mirtazapine, venlafaxine and bupropion (23). This seems to be particularly evident for bupropion with up to 90% reduction in AUC when CBZ was added to a stable regime of 150 mg (27). VPA has no effect on bupriopion metabolism but seems to slightly increase the plasma levels of the active metabolite of venlafaxine, O-desmethylvenlafaxine (28).

Compared to first-generation AEDs, new compounds have a better pharmacokinetic profile with a low risk of interactions. Oxcarbazepine (OXC) and topiramate (TPM) may have weak inducing properties, especially at high doses. A single study documented a possible interaction between OXC and clomipramine (29) but systematic studies are lacking.

2.2.2 The effect of antidepressants on AEDs

Data on the effects of TCAs on AEDs metabolism are limited although it seems that none of them have clinically relevant effect on CYP enzymes. In the case of SSRIs, some of them are inhibitors of the CYP 2C9, especially fluoxetine and fluvoxamine (23), and this can obviously impact on PHT metabolism (30,31) and partially on VPA (32). Data on sertraline are contradictory as in vitro studies showed quite weak inhibition properties on CYP enzymes (33) but a few case reports documented increased serum levels for VPA (34) and lamotrigine (LTG) (35). However, a retrospective study aimed at investigating potential pharmacokinetic interactions between LTG and sertraline showed no clinically relevant changes in LTG levels (36). Paroxetine, citalopram, mirtazapine, venlafaxine and bupropion do not affect the metabolism of AEDs.

2.3 Pharmacodynamic interactions between antiepileptic and antidepressant drugs

Pharmacodynamic interactions are rarely systematically studied. In general terms, they can be divided into positive and negative. Positive interactions represent additive or synergistic treatment effects and this can be potentially postulated for depression, anxiety, pain and migraine prophylaxis, but evidence-based data are limited. For example, pregabalin (PGB) is currently licensed for the treatment of generalised anxiety disorder and a recent study suggested a synergistic effects between antidepressants and PGB (37). Evidence-based data on augmentation strategies in neuropathic pain or migraine are limited although it is reasonable to hypothesise that the combined AED-antidepressant treatment could be favourable. Pharmacodynamic interactions are often discussed in the context of side effects but it is important to emphasise that there are no systematic studies on this regard. It is obvious to speculate that antidepressant-AED combinations can be associated, in selected cases, with increased risk of sedation, weight gain or other side effects. The relative activity of the individual compound on different receptor groups is of great relevance in this context and different antidepressants can have a different spectrum of activity even if they belong to the same antidepressant group (**Figure 1**). **For example, it is well known that the muscarinic block (especially M1 receptors) can be associated with dry mouth, paradoxical excessive perspiration, constipation, blurred vision, mydriasis, metallic taste, and urinary retention while orthostatic hypotension are due to the alpha receptor blockade (especially alpha 1). Anti-histaminergic compounds are associated with drowsiness, sedation, and weight gain while sexual dysfunction, loss of libido, impaired erection or ejaculation, and anorgasmia are due to overactivation of 5-HT2 receptors** (24). Individual TCAs or SSRIs have different activity on these receptors being responsible for a different spectrum of side effects and, as a consequence, a different risk of negative pharmacodynamic interactions (**Table2**).

2.4 Effect of antidepressants on seizure threshold

That antidepressants may lower the seizure threshold leading to seizure exacerbation has represented for a long time a major concern. However, this was based on *a priori* assumption rather than on clinical evidence. The story of the association between antidepressants and seizures goes back to the 1950s and 1960s when a number of case reports documented epileptic seizures in patients treated with TCAs, especially imipramine (38,39). Subsequently EEG studies showed also activation of the EEG and epileptic abnormalities with amitriptyline and imipramine (40,41). This data, despite not systematic and based just on a few specific agents, led to the general impression that all antidepressants were proconvulsants. In reality, the issue of drug-related seizures is quite complex and it is not only confined to psychotropic medications. In general terms, multiple factors have to be taken into account (**Table 3**) and, on the contrary, studies in animal models suggest that serotonin potentiation is anticonvulsant (42–44).

Among all antidepressants, maprotiline, high dose of clomipramine and amitriptyline (>200mg) and high doses of bupropion immediate release formulation (>450 mg) seem to be more frequently associated with seizures than others (21) (**Table 4**). However, it is important to bear in mind that current knowledge on seizure prevalence during antidepressant drug treatment is based on psychiatric populations and it is still unknown whether this data can be transferred to patients with epilepsy and whether some epileptic syndromes are more at risk than others (45). This point is of great relevance if we consider the increased prevalence of seizures in patients with mood disorders (46,47). In fact, it is now clear from epidemiological studies that the relationship between epilepsy and depression is bidirectional, meaning that not only patients with epilepsy are at increased risk of depression but also patients with mood disorders are at increased risk of epileptic seizures (6). If we take into account such an increase risk, the reported prevalence of epileptic seizures during treatment with antidepressants in patients with mood disorders (48) is, for the majority of compounds, lower than the expected (**Table 4**).

2.5 The use of lithium in epilepsy

The use of lithium in epilepsy is very rarely considered as a number of antiepileptic drugs are also considered first line treatment in bipolar disorder (e.g. VPA). In case lithium is needed, interactions with some specific AEDs have to be considered. In fact, the concomitant prescription of lithium and CBZ is associated with increased lithium toxicity, especially thyroid toxicity (49), as well as a severe hyponatraemia when lithium is discontinued (50). The concomitant prescription with VPA is associated with increased risk of tremor, sedation and weight gain (21) while TPM can reduce the clearance of lithium leading to toxic levels (51). For other AEDs, especially LTG, there are no specific concerns and the combination should be well tolerated.

In terms of proconvulsant effect, this seems to be a concern only in the context of toxicity. The majority of labs consider a therapeutic level between 0.4 mmol/l and 0.8 mmol/l for the prophylactic treatment of mood episodes and between 0.6 mmol/l and 1.0 mmol/l for the acute treatment of mania. In the majority of cases, symptoms of toxicity starts for levels above 1.5 mmol/l but it is advisable to maintain always concentrations below 1.0 mmol/l. Seizures have been reported in the context of overdose with serum levels higher than 3 mmol/l, while within the therapeutic levels, the effect of lithium on seizure frequency in individuals with epilepsy is inconsistent (52). If lithium is

needed and indicated, vigilant monitoring of blood levels and careful clinical follow up are warranted.

3. ANXIETY DISORDERS

3.1 Evidence from RCT in epilepsy

If the number of studies on the treatment of depression in epilepsy is very limited, there are no controlled studies at all about treatment of anxiety disorders in epilepsy. The Commission on Neuropsychiatry of the International League Against Epilepsy published a collection of papers about treatment strategies in adults with epilepsy and psychiatric disorders (19) and one paper was dedicated to the treatment of anxiety disorders (53). **In general terms, it is reasonable to adopt therapeutic protocols recommended in patients with anxiety disorders considering the specific needs of patients with epilepsy (Table 5). SSRIs and cognitive behavioural therapy (CBT) can be considered first line treatment in patients with epilepsy and panic disorder. PGB can be considered first choice in patients with epilepsy and generalised anxiety disorder given the amount of clinical data.** In social anxiety disorder and post-traumatic stress disorder, SSRIs can be considered first choice, in particular sertraline and paroxetine due to the low impact for interactions and the favourable tolerability. For obsessive compulsive disorder CBT is considered first line treatment. When drug treatment is needed, SSRIs, in particular sertraline, have to be preferred.

Although it is reasonable to embrace standardized protocols of treatment developed for people with anxiety without epilepsy, it is also evident that psychiatric disorders of epilepsy present, more often not, with atypical features (54,55) that may require individualised approaches. For this reason, studies in patients with epilepsy are anyway urgently needed.

4. PSYCHOSES

4.1 Evidence from RCT in epilepsy

Antipsychotic drugs can be divided into first-generation (FGAP) and second-generation (SGAP) compounds (**Table 6**). SGAP have progressively replaced old compounds in developed countries due to favourable long term tolerability (e.g. reversible extrapyramidal symptoms and low rates of tardive dyskinesia). However, it is important to bear in mind that there is no clear evidence that one generation is more or less effective than the other. In the absence of specific treatment guideline, psychotic symptoms in the context of an interictal psychosis (IIP) should be treated in line with well-established treatment protocols for primary schizophrenia and related psychoses (56). As already discussed for mood and anxiety disorders, the Commission on Neuropsychiatry of the International League Against Epilepsy published a collection of papers about treatment strategies in adults with epilepsy and psychiatric disorders (19) and one paper was dedicated to the treatment of psychoses (57).

Psychotic symptoms in IIP can be difficult to manage for a variety of reasons that commonly include poor response to treatment, individual differences in tolerability to antipsychotic drugs, potential interactions with AEDs and effect on seizure threshold, the individual's adherence to psychiatric treatment (57). In addition, it has to be considered that at least 50% of patients are partially or completely non-adherent to treatment (57,58) and approximately 15% of IIP episodes may remit with no antipsychotic treatment (59).

4.2 Pharmacokinetic interactions between antiepileptic and antipsychotic drugs

4.2.1 The effect of AEDs on antipsychotics

As already discussed for antidepressants, first generation AEDs which induce CYP enzyme activity are burdened by a number of interactions. CBZ reduces the plasma levels of all antipsychotics (60) and regarding SGAP this has been shown for aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone (61). This interaction is particularly evident for quetiapine which is mainly metabolised by the CYP 3A4. In fact, the introduction of CBZ can lead to undetectable serum concentrations of quetiapine even at dosages of 700 mg per day (62). Oxcarbazapine (OXC) is a keto-analog of CBZ but seems to be a modest CYP 3A4 inducer, for this reason pharmacokinetic interactions with antipsychotics are usually not clinically relevant.

As far as all other AEDs are concerned, they do not seem to have a major impact on SGAP metabolism. Individual differences in treatment response have to be carefully considered especially for drugs like olanzapine and clozapine that have a complex metabolism with multiple enzymatic pathways involved. Although VPA is usually regarded as an inhibitor, there are no reports of increased antipsychotic drug serum levels when prescribed in combination. Conversely, VPA seems to mildly induce, in some selected cases, the metabolism of some SGAP (i.e. olanzapine, aripiprazole, clozapine, quetiapine) (61). These interactions are rarely clinically relevant and should be considered on an individual basis.

4.2.2 The effect of antipsychotics on AEDs

In general terms, both FGAP and SGAP do not seem to have major influence on enzymatic pathways leading to interactions with AEDs.

4.3 Pharmacodynamic interactions between antiepileptic and antipsychotic drugs

As already discussed for antidepressants, data on pharmacodynamic interactions is generally limited. Favourable pharmacodynamic interactions between SGAP and AEDs, especially VPA, comprise well known augmentation strategies for the treatment of mania (63,64). The combined prescription of TPM or zonisamide (ZNS) may represent another possible favourable pharmacodynamic interaction as both AEDs may reverse SGAP-induced weight gain (61,65). Negative pharmacodynamic interactions are not systematically studies. In general terms, those that can be considered clinically relevant include increased sedation, weight gain and hematologic problems. Additive sedation with antipsychotics seems to be relevant for all first generation AEDs and TPM. Additive weight gain is particularly evident for the combination of VPA and olanzapine (66) but it should be considered when olanzapine is combined with any AED associated with this side effect such as CBZ, gabapentin (GBP) and pregabalin (PGB) (67). CBZ-clozapine combination is not recommended due to the increased risk of agranulocytosis but it is recommended to be clinically vigilant for possible leukopenia when VPA is coprescribed with clozapine or olanzapine (61).

4.4 Effect of antipsychotics on seizure threshold

While the supposed proconvulsant effect of antidepressants is still matter of debate, this seems to be established for antipsychotics. However, it has to be acknowledge that this has been demonstrated mainly for clozapine while all other antipsychotics, especially SGAP, seem to have a

low proconvulsant risk (48). For clozapine the risk seems to be both titration- and dose-dependent. A US case series documented a mean prevalence of seizures during clozapine treatment of 2.9% with prevalence rates of 1%, 2.7% and 4.4% for dosages of <300 mg, 300-600 mg and >600 mg respectively (68). Prevalence rates are much lower in patients without a previous history of seizures (69) confirming that clozapine can deteriorate seizures in predisposed individuals. Up to 5% of patients treated with clozapine can have EEG abnormalities (70) but whether this is a predictive factor for clozapine-induced seizures is still unknown. In general terms, clozapine seems to deteriorate mainly myoclonic jerks but generalised tonic clonic seizures or even focal seizures have been reported in predisposed individuals (70). Chlorpromazine is another antipsychotic with an increased risk of seizures but this seems to be a major concern only for high doses (>1000 mg/day) which are rarely used in clinical practice (45). Apart from clozapine, SGAP seem to be generally safe in people with epilepsy but careful clinical monitoring is always advised.

5. ATTENTION DEFICIT HYPERACTIVITY DISORDER

5.1 Evidence from RCT in epilepsy

Epidemiological studies consistently show that attention deficit hyperactivity disorder (ADHD) is 2 to 3 times more common in people with epilepsy than in the general population (1,71). Demographic data shows an equal male-female ratio in epilepsy whereas males are more often affected in samples with isolated ADHD as seen in paediatric clinics (71). Despite the limited number of studies investigating ADHD subtypes in epilepsy, there seems to be more inattentive presentations in patients with epilepsy as compared to ADHD in psychiatric samples.

Guidance of treatment of ADHD outside epilepsy recommends either methylphenidate or amphetamine, switching to the stimulant not previously used if the patient fails to respond or has side effects, and atomoxetine as second line agent if stimulants are not effective or cause adverse effects (72). In general terms, there is more data on methylphenidate than amphetamine in patients with epilepsy and ADHD. Three randomised, double-blind, placebo-controlled, cross-over trials showed that methylphenidate 0.3-1 mg/kg/day is effective and well tolerated in children with epilepsy and ADHD with response rates ranging between 60% and 70% (73–75). For amphetamine, there is just a retrospective study of 36 patients with epilepsy and ADHD that compared response rates of amphetamine and methylphenidate and showed a significant improvement in 63% of patients taking methylphenidate versus 24% of those on amphetamine (76).

In case methylphenidate fails guidelines of treatment would recommend atomoxetine but data in patients with epilepsy are more than scant with just a retrospective study documenting up to 63% discontinuation rates mainly due to inefficacy (77).

5.2 Pharmacokinetic interactions between antiepileptic drugs and psychostimulants

Despite early reports about possible interactions between methylphenidate and first generation antiepileptic drugs (78,79), there is no data suggesting clinically relevant interactions with AEDs. In general terms, methylphenidate seems to have a moderate inhibitory effect on CYP enzymatic pathways (80) and for this reason clinical monitoring in individual cases is advisable.

5.3 Effect of psychostimulants on seizure threshold

Historically, psychostimulants have represented the class of medications most frequently alleged to trigger seizures. However, especially for methylphenidate, clinical data from both RCT and open trials clearly suggests that this is not the case as no seizure worsening has been demonstrated in any single trial (73–75,81). Data on amphetamines are very limited (82).

6. CONCLUSIONS

Psychiatric disorders represent frequent comorbidities in patients with epilepsy affecting quality of life, morbidity and mortality (83). Evidence-based data on the management of these conditions are limited but a number of recommendations are now available to guide clinical practice. Careful clinical monitoring is always advisable and the "start low go slow" recommendation still represents the best practice bearing in mind that low starting doses do not necessarily mean low target doses. **Continuous monitoring of quality of life of patients is always advisable (84) and full remissions from psychiatric symptoms should always be the ultimate goal as many studies demonstrated that subthreshold or residual symptoms still affect quality of life of patients with epilepsy (85).**

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Table 1. Classification of psychiatric symptoms according to their temporal relation with seizures.

PERI-ICTAL	**PRE-ICTAL** **ICTAL (Focal seizures with psychic symptoms)** **POST-ICTAL**
INTER-ICTAL	**Unrelated to seizure occurrence**

Table 2. Spectrum of side effects and potential negative pharmacodynamic interactions.

	Sedation	**Weight gain**	**Hyponatraemia**	**Arrhythmias**	**Sexual dysfunction**	**Urinary retention**	**Osteoporosis**	**Bleeding**
ADs	TCAs Trazodone Mirtazapine	TCAs Mirtazapine Paroxetine	SSRIs	Citalopram Fluoxetine Sertraline Duloxetine Reboxetine Venlafaxine	SSRIs TCAs	TCAs Paroxetine Mirtazapine	SSRIs	SSRIs
AEDs	All except Felbamate Lacosamide Lamotrigine Tiagabine	Carbamazepine Valproate Gabapentin Pregabalin Retigabine	Carbamazepine Oxcarbazepine Eslicarbazepine	Felbamate Retigabine	Carbamaze pine	Retigabine	Carbamazepine Barbiturates Phenytoin Valproate Topiramate	Valproate

ADs = antidepressant drugs; AEDs = antiepileptic drugs

Table 3. Risk factors for drug-related seizures.

Patient-related	History of epilepsy Family History of epilepsy Brain disorder (post-natal brain damage, head injury, dementia)
Treatment-related	High-dose or overdose Rapid titration Abrupt withdrawal (i.e. benzodiazepines or antiepileptic drugs) Pharmacodynamic interactions (i.e. effect on seizure threshold) Pharmacokinetic interactions (i.e. inhibition -> overdose/high-dose)

Table 4. Prevalence of seizures with antidepressant drugs.

DRUG	DOSE	REPORTED (%)	EXPECTED (%)
Amitriptyline	<200 mg >200 mg	0.1 0.6	0.25 (95%CI 0.20-0.35)
Imipramine	50-600 mg	<0.1-0.9	
Clomipramine	>200 mg	0.5	
Maprotiline	150-200 mg	0.4	
Fluoxetine	20-60 mg	0.2	
Fluvoxamine	<100 mg	0.2	
Sertraline	50-100 mg	<0.1	
Paroxetine	20-60 mg	0.1	
Bupropion	300 mg SR 300-450 mg IR >450mg IR	0.1 0.4 >0.6	
Mirtazapine	30 mg	<0.1	

Table 5. Treatment of anxiety disorders in epilepsy.

Panic attack disorder	1. SSRIs (any) + CBT or CBT alone
Generalized anxiety disorder	1. Pregabalin 2. Paroxetine, Venlafaxine, Imipramine
Social anxiety disorder	1. SSRIs (sertraline, escitalopram, paroxetine)
Post-traumatic stress disorder	1. SSRIs (sertraline, paroxetine)
Obsessive-compulsive disorder	1. CBT 2. CBT + sertraline 3. CBT + clomipramine

CBT = Cognitive behavioural therapy

Table 6. Classification of antipsychotic drugs.

First Generation Antipsychotics
Chlorpromazine
Droperidol
Fluphenazine
Haloperidol
Loxapine
Perphenazine
Pimozide
Prochlorperazine
Thiothixene
Thioridazine
Trifluoperazine
Second Generation Antipsychotics
Aripiprazole
Asenapine
Clozapine
Iloperidone
Olanzapine
Paliperidone
Quetiapine
Risperidone
Ziprasidone

Figure Legend

Figure 1. Spectrum of activity of SSRIs on different receptors. 5HT = serotonin receptor; DRI = dopamine reuptake inhibition; SRI = serotonin reuptake inhibition; H = histamine receptors; NRI = noradrenaline reuptake inhibition; NOS = Nitric oxide synthesis; M = Muscarinic receptors; σ = opioid receptor

Supplementary Material. Definition and criteria for side effects and their relevance for seizures as a side effect of antidepressants.