EPILEPSY AND PSYCHIATRIC COMORBIDITIES: DRUG SELECTION

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ABSTRACT/OPINION STATEMENT

Purpose of review: The pharmacological treatment of patients with epilepsy and psychiatric comorbidities may sometimes represent a therapeutic challenge. This review is focused on the pharmacological management of patients with epilepsy and psychiatric problems in terms of rationalization of the antiepileptic drug (AED) treatment and the pharmacological management of the most clinically relevant psychiatric comorbidities, namely mood and anxiety disorders, psychoses and attention deficit hyperactivity disorder (ADHD). **Recent findings:** Up to 8% of patients with drug-resistant epilepsy develop treatment-emergent psychiatric adverse events of AED regardless of the mechanism of action of the drug and this is usually related to an underlying predisposition given by the previous psychiatric history and the involvement of mesolimbic structures. Careful history taking, periodic screening for mood and anxiety disorders, low starting doses and slow titration schedules can reduce the possibility of AED-related problems. A pragmatic checklist for the pharmacological management of patients with epilepsy and psychiatric disorders is presented. **Summary:** Patients should be informed of potential behavioral effects of AEDs but no drugs should be excluded *a priori*. Any psychiatric comorbidity should be addressed in the appropriate setting and full remission and recovery should always represent the first goal of any therapeutic intervention. Neurologists should be aware of side effects of major psychotropic drug classes in order to fully counsel their patients and other health professionals involved.

INTRODUCTION

Epilepsy is one of the most frequently encountered neurological condition with incidence rates, in high-income countries, ranging between 40 and 70/100000/year [1,2] while in low income countries the incidence is higher and up to 120/100000/year [3]. Prevalence studies have reported lifetime rates for epilepsy ranging between 4 and 10 /1000 in high-income countries [4] but in selected rural areas it is reported up to 57/1000 [5]. The majority of people with epilepsy live a normal life but there is no doubt that the long-term prognosis of epilepsy is poor due to the increased morbidity and mortality [6]. This can be due to physical problems (e.g. fractures and injuries), comorbidities with other systemic and neurological diseases (e.g. stroke, diabetes) as well as psychosocial problems [7]. It is estimated that epilepsy accounts for the 0.5% of the total burden of diseases [8] but the impact of comorbidities has never been taken into account.

The International League Against Epilepsy (ILAE) pointed out that epilepsy is a disorder of the brain characterized not only by recurrent seizures, but also by its neurobiological, cognitive, psychological and social consequences [9], emphasizing the long-term psychosocial issues and the high prevalence of psychiatric and behavioral problems affecting these patients. In general terms, psychiatric disorders show a uniformly increased prevalence in epilepsy as compared to the general population, with mood and anxiety disorders being the most frequently encountered problems among adults [10,11] while in children developmental issues (i.e. intellectual disabilities and autism) represent the major comorbidities [12]. In addition, epidemiological studies have shown that the relationship between epilepsy and behavioral problems is more complex than expected as not only people with epilepsy are at increased risk of developing psychiatric disorders but patients with psychiatric disorders are also at increased risk of developing epilepsy [13]. The so-called bidirectional relationship between epilepsy and psychiatric disorders [14] has been established not only for depression [15–17] but also for schizophrenia [18–20] and autism [21,22]. All these data taken together seem to suggest that some patients develop a complex neuropsychiatric condition characterized by a clinical phase dominated by psychiatric symptoms followed by the development of epilepsy. Whether psychiatric problems are part of a complex neuropsychiatric disorder, a consequence of having epilepsy or simply due to the unlucky occurrence of two conditions in the same patient, there is no doubt that the management of these patients can be quite challenging. For this reason, epileptologists need to develop multiple clinical skills and to organize a network of different health care professionals (i.e. psychiatrists, clinical psychologists, neuropsychologists, social workers and occupational therapists) in order to provide the best treatment for patients with epilepsy [23]. This is a narrative review focused on the pharmacological management of patients with epilepsy and psychiatric problems in terms of rationalization of the antiepileptic drug (AED) treatment and the pharmacological management of the most relevant, either epidemiologically or clinically, psychiatric conditions.

SHOULD PSYCHIATRIC COMORBIDITIES INFLUENCE AED CHOICE IN EPILEPSY?

It is now established that the effect of AEDs is not only restricted to the modulation of cortical excitability but they also modulate systems that regulate mood and behavior [24]. It is also established that AEDs are associated with treatment-emergent behavioral problems that are reported not as frequently as in epilepsy, when AEDs are used in other conditions such as pain, migraine or movement disorders [25]. It has been also reported that about 8% of patients with drug-resistant epilepsy develop treatment-emergent psychiatric adverse events regardless of the mechanism of action of the individual AED and this is apparently driven by the underlying psychiatric comorbidity [26]. Data from people with new onset epilepsy are more than scant, although it is reasonable to hypothesize that these problems happen less frequently than in patients with drug-resistant epilepsies [27].

In general terms, the psychotropic potential of any central nervous system (CNS) agent correlates with the mechanism of action, for example GABAergic drugs are more sedative than voltage-gated channel blockers, but this does not always apply to patients with epilepsy as the final psychotropic effect clearly arises from the interaction between the drug and the epileptic brain. In fact, patients with temporal lobe epilepsy and an early onset temporolimbic dysfunction, as suggested by a history of febrile convulsions, have, for example, an almost 4-time increased risk of developing depression with topiramate [28]. Still, some patients develop severe psychiatric reactions when their seizures are rapidly controlled or their EEG normalized, a phenomenon known as the Landolt's phenomenon [29]. Finally, while some AEDs (i.e. valproate, carbamazepine, lamotrigine) are successfully used for the treatment of mood disorders outside epilepsy [24], the same AEDs may be associated with paradoxical mood deterioration in people with epilepsy [30,31]. A recent systematic review focusing on aggressive behavior, as a treatment emergent problem, shows that more than 50% of examined AEDs are associated with aggressive behavior as a treatment emergent adverse event in 1% to 10% of cases, and among identified AEDs, some of them are successfully used as mood stabilizers or anxiolytics outside epilepsy like valproate, lamotrigine, pregabalin or clobazam [31]. All these data taken together clearly suggest that, in patients with epilepsy, the psychiatric comorbidity represents the fertile ground on which these paradoxical reactions develop [30] and suggest few practical points that can help clinicians in managing these problems: i) the previous psychiatric history and the family psychiatric history should be always part of a comprehensive epileptological review; ii) all patients with epilepsy should be periodically screened for major psychiatric disorders; iii) all patients with epilepsy and their relatives should be routinely informed about the psychotropic potential of any AED when data are available; iv) in case of a previous psychiatric problem, even if currently in remission, titration rates for AEDs should be slower than those adopted in other patients with no previous behavioral problems (**Table 1**).

The rapidity of the titration rate is an important point in order to avoid side effects and not to preclude the opportunity of good seizure control in patients requiring specific AEDs or specific AED combinations for their epilepsy syndrome. In fact, even if it is true that some compounds seem to be more frequently associated with behavioral problems than others

[24,30,32], it is also established that the rapidity of the titration schedule represents one of the most important variables [33,34] and this is even more important when other risk factors are present. A retrospective study in a large cohort of consecutive patients treated with topiramate shows that while a previous history of depression is associated with a 3.5-times increased risk of developing depression as a treatment emergent adverse event, the use of a rapid titration schedule on top of a previous history of depression is associated with a 23-times increased risk [28]. In conclusion, even if it is established that some AEDs are more likely to be associated with treatment emergent problems than others, the way they are used can minimize such a risk. Patients should not have precluded the opportunity of trying an efficacious treatment just because they are at increased risk. It is important to explain these risks to patients and their relatives and to inform them that it is possible to reduce such risks adopting slow titration rates.

PSYCHOPHARMACOLOGICAL TREATMENT IN EPILEPSY: WHAT'S THE DRUG OF CHOICE?

The optimal management of psychiatric comorbidities in epilepsy should be based on the identification of patients at risk, through a careful history taking, and the early identification of psychiatric complications, through a periodic screening. A number of clinical instruments have been validated in patients with epilepsy especially for the detection of mood and anxiety disorders [35]. The Neurological Disorders Depression Inventory for Epilepsy (NDDIE) [36] and the Generalized Anxiety Disorder 7 (GAD7) [37] showed to be very practical and user-friendly screening instruments in an outpatient setting to identify a major depressive episode and anxiety disorders. However, psychiatric problems are, more often than not, ignored and go untreated, unless they are severe enough to cause major disability. This is often due to the paucity or total lack of knowledge of the individual neurologist about psychotropic medications and how to use them [38]. During the last few years the ILAE has issued a number of publications regarding a pragmatic approach to these problems based on evidence from primary psychiatric disorders that should help clinicians in approaching these problems in a standardized way [39,40].

Mood and anxiety disorders

Antidepressants are considered first line treatment for major depression and the majority of anxiety disorders in conjunction with cognitive behavioral therapy. Antidepressants can be classified into first generation agents such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) and second generation drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) and other antidepressants with varying mechanisms of actions [41] (**Table 2**). The only double-blind trial of antidepressants in epilepsy was published more than 30 years ago and compared nomifensine and amitriptyline with placebo [42]. Since that time, a number of open studies, mainly using SSRIs, in small samples of unselected patients with epilepsy have been published [41,43]. Despite not being controlled trials, all these studies

taken together show that SSRIs are safe and well tolerated in people with epilepsy. Historically, the effect of antidepressants on seizure threshold has represented a major concern for clinicians. However, this was grounded on an *a priori* assumption based on early anecdotal reports of patients developing epileptic seizures during treatment with some drugs [44] and EEG studies showing epileptic abnormalities during treatment with TCAs [45,46]. Subsequent studies clarified that the supposedly increased seizure risk was genuine for a few specific compounds [47] while, on the contrary, serotonin potentiation is even anticonvulsant [48,49]. Data from controlled trials and clinical studies in patients with depression outside epilepsy show that maprotiline, high doses of TCAs (>200 mg daily), especially amitriptyline and clomipramine, and high doses of bupropion (>450 mg) are associated with an increased risk of seizures [41,47]. Data regarding SSRIs show that they are not only safe in terms of seizure risk but there are also enough reports in patients with epilepsy regarding sertraline [50,51] and citalopram [52,53] to consider them first line treatment in patients with epilepsy and depression. Among other SSRIs, fluoxetine and fluvoxamine are generally not recommended mainly because of the risk of drug-drug interactions and the complex pharmacokinetics. In fact, both of them have an inhibitory effect on the CYP2C9 which may be associated with an increased risk of pharmacokinetic interactions with AEDs metabolized by this enzymatic pathway like phenytoin and partially valproate [41,54]. In terms of other potential pharmacokinetic interactions, clinicians should bear in mind that first generation AEDs like carbamazepine, phenytoin and barbiturates are potent inducers leading to at least 25% reduction in plasma levels of almost all SSRIs [41]. It is still unclear whether this is clinically relevant, but clinical monitoring is recommended in order to achieve full remission from depressive symptoms. In fact, while low starting doses may be considered reasonable in complex patients with multiple treatments, it should be always kept in mind that this does not mean low target doses and full remission should always be the first goal of an antidepressant treatment.

The management of side effects of antidepressants is another relevant point for clinicians. In fact, while neurologists may be familiar with data on seizures during antidepressant treatment, they are very rarely aware of the spectrum of side effects of antidepressants and the potential for pharmacodynamic interactions with AEDs. Hyponatraemia, weight gain, sexual dysfunction, extrapyramidal symptoms, bone loss and bleeding are recognized side effects of SSRIs and for this reason careful clinical monitoring is recommended with specific drug combinations: i) SSRIs-carbamazepine, oxcarbazepine and eslicarbazepine (hyponatraemia); ii) citalopram-valproate, carbamazepine (weight gain); iii) SSRIs-valproate (extrapyramidal symptoms); iv) SSRIs-carbamazepine (sexual dysfunction in males); v) SSRIs-carbamazepine, barbiturates, phenytoin, valproate and topiramate (bone loss); vi) SSRIs-valproate (bleeding) [41].

Psychoses

Psychoses represent a rare but severe problem in patients with epilepsy and should be always managed in a psychiatric setting. However, it is important that epileptologists are able to counsel patients and colleagues about the potential effect of antipsychotic drugs on seizure threshold and whether specific drugs should be preferred. Antipsychotic drugs are usually

classified into first (FGAP) and second generation drugs (SGAP). SGAPs are increasingly used because of their favorable profile in terms of long-term side effects with low rates of extrapyramidal symptoms. Data from controlled trials and open studies in patients with psychoses outside epilepsy show that only clozapine has a significantly increased risk of seizures [47]. A US case series showed that seizures during treatment with clozapine are clearly dose-dependent with a seizure prevalence of 1%, 2.7% and 4.4% for dosages of <300 mg, 300-600 mg and >600 mg respectively [55,56]. EEG abnormalities are reported in up to 5% of patients treated with clozapine [57] but it is still unknown whether these abnormalities represent a risk factor for clozapine-related seizures. In general terms, SGAP should be preferred to FGAP mainly because of the better long term tolerability but there is no evidence supporting the use of one drug rather than another. Risperidone and aripiprazole are often considered drug of choice in patients with epilepsy because of the amount of data in patients with autism showing no increased prevalence of seizures [58] but there is no real evidence favoring one drug to the other and most of the time the drug of choice is based on the experience of the individual clinician. For this reason, psychiatrists managing psychotic disorders in epilepsy should always follow guidelines of treatment outside epilepsy. In case clozapine is needed, slow starting doses, low titration rates and careful clinical monitoring are recommended.

As already mentioned for antidepressants, psychiatrists need to be bear in mind that first generation AEDs (i.e. barbiturates, carbamazepine and phenytoin) induce the CYP system reducing the plasma levels of all antipsychotics and, for this reason, doses of the antipsychotic should be always adjusted according to clinical response [41] and careful attention is needed when the AED is discontinued to avoid antipsychotic-related toxicity [41]. This interaction is particularly evident for quetiapine where the combined treatment with carbamazepine leads to undetectable levels of the antipsychotic for doses up to 700 mg [59]. Regarding clozapine and olanzapine, both of them have a complex metabolism mediated by a number of different enzymatic pathways and for this reason a low starting dose and a slow titration regime should be always recommend [41,60]. In terms of potential side effects, clinicians should be aware of weight gain particularly with olanzapine and leukopenia with clozapine [41].

Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD) has an estimated prevalence of 3.4% in high-income countries and shows high comorbidity rates with other neurodevelopmental disorders such as autism and intellectual disabilities [61]. Until recently, few outcome studies beyond the third decade of life were available but new epidemiological studies show that the long-term prognosis of ADHD is poor with only 35% of patients going into remission during adulthood and an increased risk of substance abuse and antisocial personality disorder, increased psychiatric admission, incarceration and mortality [61]. A prospective community based study in South West England shows that up to one third of children and adolescents with active epilepsy also has ADHD [12]. It is now established that ADHD is 2 to 3 times more frequent in epilepsy than in the general population and it is usually characterized by a more inattentive presentation and an equal male to female ratio [62]. A community-based

survey in more than 1000 adult patients with epilepsy reports ADHD-like symptoms in 1 out of 5 subjects and suggest a strong correlation with depression, anxiety, drug-resistance and poor quality of life [63].

The majority of international guidelines include methylphenidate, atomoxetine and dexamphetamine as pharmacological options [64,65]. According to the NICE guidelines methylphenidate is the drug of choice in children with severe symptoms and/or comorbidities and should be always considered first line treatment in adults with ADHD [65]. Historically, neurologists have been reluctant to prescribe psychostimulants in patients with epilepsy but data from three randomized, double-blind, crossover trials show that methylphenidate 0.3-1 mg/kg/day is well tolerated with no evidence of seizure worsening and response rates range between 60% and 70% [66–68]. Data on potential pharmacokinetic interactions with AEDs are unavailable apart from reports suggesting a potential inhibitory effect of methylphenidate on the CYP system [69]. For this reason, low starting doses, slow titration rates and clinical monitoring are advisable.

Data about atomoxetine and amphetamines in epilepsy are mainly anecdotal [41] and for this reason, in case of no response to methylphenidate, parents should be informed and clinical monitoring is needed. All children with epilepsy and ADHD should be reviewed in a specialist Epilepsy Transition Service in order to fully clarify whether ADHD is in remission or not [70].

CONCLUSIONS

The pharmacological treatment of patients with epilepsy and psychiatric comorbidities may be quite challenging. In general terms, patients should be informed of potential side effects of AEDs but no drugs should be *a priori* excluded Careful history taking and periodic screening for common problems, such as mood and anxiety disorder, can help clinicians in identifying those at increased risk and adopt low starting doses and slow titration schedules of the AEDs as this practice can significantly lower the possibility of treatment-emergent psychiatric problems.

For mood and anxiety disorders, citalopram and sertraline can be reasonably considered first line treatment bearing in mind that low starting doses do not represent low target doses and full remission and recovery from depression should always be the first goal of the antidepressant treatment. Neurologists should also be aware of major side effects of SSRIs in order to fully counsel their patients. Patients with epilepsy and psychotic disorders should have access to the same treatment strategies that are successfully used outside epilepsy bearing in mind the potential for pharmacokinetic interactions and the increased risk of seizures with clozapine. However, this option should not be precluded to patients with epilepsy, if clinically indicated in the specific psychotic disorder. Finally, children with epilepsy and ADHD should always have access to the same standard of care of children with ADHD outside epilepsy considering the deleterious long-term consequences of untreated

ADHD. If needed, methylphenidate represents a safe and effective option in children with epilepsy.

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Conflict of interests

Human and animal rights and informed consent

This is not a study involving human or animal subjects.

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Table 1. Checklist for patients with epilepsy and psychiatric comorbidities

Previous history of psychiatric disorders documented	[]
Family history of psychiatric disorders documented	[]
Screening for current psychiatric problems done (e.g. NDDIE, GAD-7)	[]
Discussed about potential treatment-emergent psychiatric problems of AEDs	[]
Low starting dose and slow titration regime for AED in place	[]
Treatment/referral for current psychiatric problem in place	[]
Potential interactions/side effects of psychotropic treatment discussed	[]

Table 2. Psychotropic drug classes and main treatment issues in patients with epilepsy and psychiatric comorbidities.

PSYCHOTROPIC DRUG CLASSES	PSYCHOTROPIC DRUGS (in bold treatment of choice)	TREATMENT ISSUES IN EPILEPSY
ANTIDEPRESSANTS		
Reversible Inhibitors of Monoamine Oxidase A (RIMAs)	Moclobemide	Pharmacokinetic interactions with inducers (barbiturates, CBZ, PHT). Increased seizure risk
Tricyclic antidepressant drugs (TCAs)	Amitriptyline, Clomipramine, Desipramine, Imipramine, Maprotiline, Nortriptyline, Protriptyline, Trimipramine	Pharmacokinetic interactions with inducers (barbiturates, CBZ, PHT) Increased risk of weight gain, urinary retention, sexual dysfunction, sedation Increased risk of seizures for high doses (>200 mg)
Selective Serotonin Reuptake Inhibitors (SSRIs)	**Citalopram**, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, **Sertraline**	Pharmacokinetic interactions with inducers (barbiturates, CBZ, PHT) Increased risk of sexual dysfunction, hyponatraemia. Weight gain (citalopram)
Selective Noradrenergic Reuptake inhibitors (NRIs)	Reboxetine	Pharmacokinetic interactions with inducers (barbiturates, CBZ, PHT)
Norepinephrine and Dopamine Reuptake Blockers (NDRIs)	Bupropion	Pharmacokinetic interactions with inducers (barbiturates, CBZ, PHT) Increased seizure risk for high dosages (>450 mg) for immediate release formulation
Dual Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)	Duloxetine, Venlafaxine	Pharmacokinetic interactions with inducers (barbiturates, CBZ, PHT)
Norepinephrine and Specific Serotoninergic Antidepressants (NaSSAs)	Mianserine, **Mirtazapine**	Pharmacokinetic interactions with inducers (barbiturates, CBZ, PHT) Increased risk of sedation and weight gain
Dual Serotonin type 2 receptor	Nefazodone, Trazodone	Pharmacokinetic interactions with inducers (barbiturates,

Antagonists/Serotonin Reuptake Inhibitors (SARIs)		CBZ, PHT) Increased risk of CBZ toxicity with Nefazodone
ANTIPSYCHOTICS		
First Generation Antipsychotics	Chlorpromazine, Droperidol, Fluphenazine, Haloperidol, Loxapine, Perphenazine, Pimozide, Prochlorperazine, Thiothixene, Thioridazine, Trifluoperazine	Pharmacokinetic interactions with inducers (barbiturates, CBZ, PHT) Increased risk of sedation and weight gain
Second Generation Antipsychotics	Aripiprazole, Asenapine, Clozapine, IIoperidone, **Olanzapine**, Paliperidone, Quetiapine, **Risperidone**, Ziprasidone	Pharmacokinetic interactions with inducers (barbiturates, CBZ, PHT) Increased risk of sedation and weight gain Increased risk of seizures (clozapine) Increased risk of agranulocitosis (clozapine-CBZ)
PSYCHOSTIMULANTS		
Psychostimulants	**Methylphenidate**, atomoxetine, dexamphetamine	Pharmacokinetic interactions with inducers (barbiturates, CBZ, PHT) No data about atomoxetine and dexamphetamine