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Review

Mood disorders in patients with epilepsy

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Abstract:
Epilepsy is a common disabling neurological disorder associated with increased rates of mood disorders especially depression as compared to the general population. Most antidepressants at therapeutic dosages exhibit a seizure risk. Some antidepressants may also display antiepileptic effects, especially at low doses, but the mechanism of this action is largely unknown. In general, the new antidepressants that selectively inhibit the reuptake of serotonin may cause an increase in plasma concentrations of antiepileptic drugs. On the other hand, phenobarbital, phenytoin and carbamazepine stimulate the catabolic degradation of tricyclic antidepressants and tricyclic antidepressants have an inhibitory effect on the elimination of antiepileptic drugs. This article refers to the relevance of interactions between antiepileptic drugs and antidepressant drugs in the treatment of mood disorders in patients with epilepsy.

Key words:
epilepsy, mood disorders, depression, antiepileptic drugs, antidepressant drugs

Abbreviations: 5-HT – serotonin, AD – antidepressant drug, AED – antiepileptic drug, BAD – bipolar affective disorder, CBZ – carbamazepine, DD – dysthymic disorder, GABA – γ-aminobutyric acid, MAOI – monoamine oxidase inhibitor, MDD – major depressive disorder, PB – phenobarbital, PHT – phenytoin, SSRI – selective serotonin reuptake inhibitor, TCA – tricyclic antidepressant, VPA – valproate

Introduction

Epilepsy is a chronic disorder that has important influence on human social, vocational and psychological functioning. It is known that the rate of mood disorders is higher in patients with epilepsy than in those with other chronic medical conditions, like diabetes or asthma [9, 27, 53].

Mood disorders in patients with epilepsy remain unrecognized and are very often incorrectly treated. Precise diagnosis and effective therapy are very important because of a high suicide rate. Approximately 30% to 70% epileptic patients have the incidence of depressive disorders in their lifetime [95]. Depression may have stronger influence on the quality of life than do the signs of epilepsy.

Unfortunately, in over two thirds of patients with depressive disorders, especially, when depression is associated with other medical problems, the diagnosis is missed [16, 43, 46, 53]. One of the most important reasons of such situation is the fact that both physicians and patients believe that mood disorders are the

results of a reaction to medical condition and require no treatment. In clinical settings, 43% of patients with epilepsy and major depressive disorder (MDD) and 68% with minor depressive disorder were untreated, and 38% of those who had a history of lifetime episodes of MDD had never received antidepressant treatment [130]. In a study of 44 children with epilepsy, 26% were found to have a significant depressive disorder. None of them had been diagnosed or treated with antidepressant drugs (ADs) [28].

Depressive epileptic patients often complain of symptoms that could be explained as side effects of antiepileptic drugs (AEDs) or as a result of epilepsy *per se* (Tab. 1). Such misleading complaints may involve sleep problems, changes in appetite, loss of libido, and impairment of cognition.

Tab. 1. Diagnostic criteria for depressive syndromes

Depressed mood
Feelings of worthlessness
Feelings of guilt
Loss of energy and interest [a]
Insomnia or hypersomnia [a]
Decrease or increase in appetite [a]
Loss of libido [a]
Psychomotor retardation or agitation [a]
Diminished ability to think or concentrate [a]
Suicidal ideation

[a] Known side effects of antiepileptic drugs [111]

It has been found clinically that gender is an important factor related to the depression and epilepsy [44]. Other authors have noted that more men than women with epilepsy appear to be depressed [59]. This is in opposition to what is seen in people with idiopathic depression.

Classic depressive symptoms are rare in patients with epilepsy. In the study by Mendez et al. [72], in 50% of cases, the clinical presentation of depression in patients with epilepsy was atypical. Blumer et al. [10] described a pleomorphic affective disorder in epilepsy characterized by 8 key symptoms as follows: labile depressive symptoms (depressive mood, anergia, insomnia, pain), labile affective symptoms (fear, anxiety), and supposedly "specific" symptoms (paroxymal irritability, and euphoric mood). Kanner et al. [55] preferred the term "dysthymia-like disorder of epilepsy". The author has diagnosed this disorder in 70% of depressive patients who needed treatment.

There are serious consequences of the lack of recognition and treatment of mood disorder in people with epilepsy resulting in increased morbidity and mortality. The incidence of suicide in people with epilepsy is, at least, five times higher than in the general population [4]. Prevalence of psychiatric disorders in epileptic patients and general population is shown in Table 2.

Tab. 2. Prevalence of psychiatric disorders in epilepsy [110, 111]

Psychiatric disorders	Patients with epilepsy (%)	General population (%)
Depression	11–44	2–4
Anxiety disorders	15–25	2.5–6.5
Suicide	5–10	1–2
Psychoses	2–8	0.5–0.7
Pseudoseizures	1–10	0.1–0.2
ADHD	10–40	2–10

Antiepileptic drugs (AEDs) in depression

The AEDs have measurable effects on neuronal membrane and synaptic function. Practical approaches to the drug treatment have resorted primarily to symptomatic control, i.e., suppression of seizures. Although the mechanisms of action of currently marketed ADs are still not completely understood, they ultimately involve alteration in balance between neuronal excitation and inhibition [129]. The most important, at the cellular level, mechanisms of action are [19]:

1. blocking of voltage-dependent Na^+ and Ca^{2+} channels (carbamazepine {CBZ}, gabapentin, lamotrigine, oxcarbazepine, phenytoin {PHT}, topiramate, valproate {VPA}, levetiracetam);
2. enhancement of γ-aminobutyric acid (GABA)-mediated inhibitory neurotransmission (benzodiazepines, gabapentin, phenobarbital {PB}, tiagabine, topiramate, vigabatrin, VPA);
3. reducing events mediated by excitatory amino acids (felbamate, PB, topiramate).

Many of AEDs can be classified into more than one of these three mechanistic categories [66, 68, 93].

All AEDs may provoke positive or negative psychiatric reactions in individual patients and these reactions mainly depend on the anticonvulsive strength of drugs, and person's genetic and biographic psychiatric predisposition [108]. Among a series of consecutive patients who develop a schizophreniform psychosis or major depression, 21% of depressive episodes and 15% of psychotic episodes were attributed to AED treatment, including intoxication, withdrawal syndromes, and cases of forced normalization [108]. Recent data show the link between depression and treatment with barbiturates [14, 15, 102]. There are also some suggestions that psychiatric problems are significantly increased with GABAergic substances, like vigabatrin, tiagabine or topiramate [121]. Psychoses occur in 2% of children treated with ethosuximide, and affective problems may appear as a result of treatment with CBZ [20]. PHT may cause schizophrenia-like psychoses at high serum levels [54]. Topiramate at high starting doses and rapid titration schedule also causes psychiatric adverse events in patients with epilepsy, but recent recommendations reduced the risk to develop these events [76]. Nickel et al. [78, 79] in two controlled trials have indicated that topiramate may be effective for anger and aggression associated with borderline personality disorder. Although many data suggest negative influence of AEDs on mood and behavior, these drugs are also used in a treatment of psychiatric patients. The positive psychotropic properties of CBZ and VPA are well established and frequently used in psychiatric patients [126]. Lamotrigine has antidepressant effects in patients with bipolar and rapid cycling affective disorders, and gabapentin has been used for an almost unlimited spectrum of psychiatric disorders [64]. Pregabalin has shown positive effects in insomnia and generalized anxiety disorder [83]. Levetiracetam has been demonstrated to promote depression or anxiety symptoms [35], but in contrast, two open-label trials with this drug showed improvement in mania scores of patients with bipolar spectrum disorders [6, 41].

AEDs have become very important in the treatment of manic phase of bipolar affective disorder (BAD), especially in patients with mixed states and/or rapid cycling [5]. Lithium has been used safely in patients with epilepsy and comorbid BAD [69, 114], but it is considered to be proconvulsant [71], and encephalopathy has been noted when lithium is used in combination with CBZ [49]. Lithium is effective in the prophylaxis of BAD, and it decreases the risk of suicide in these patients by more than 8-fold [39].

The risk of psychiatric complications with AEDs is likely to be related to the severity of epileptic attacks, polytherapy, rapid titration, and high doses of drugs [109]. Antiepileptic drug treatment should begin with diagnosis of the seizure and epileptic syndrome, followed by the selection of the optimal drug for an individual patient and continued with observations of both seizures and adverse effect profile [81].

Antidepressants (ADs) in epilepsy

There are four main classes of ADs (Tab. 3). The exact mechanisms of action of currently used ADs have not been elucidated as yet. The main hypothesis concerning such mechanisms is monoaminergic and mainly involves two neurotransmitters, serotonin (5-HT) and noradrenaline. Generally, depression is associated with reduced concentrations of monoamines in the brain and ADs normalize these levels.

Tab. 3. Major classes of antidepressant drugs

Tricyclics	Mono-, bi-, tetra- and heterocyclics	Monoamine oxidase inhibitors	Selective serotonin re-uptake inhibitors
Imipramine	Maprotiline	Phenelzine	Fluoxetine
Desipramine	Vilixazine	Tranylcypromine	Sertraline
Amitriptyline	Mianserin	Isocarboxazid	Paroxetine
Nortriptyline	Trazodone	Toloxatone	Citalopram
Clomipramine	Venlafaxine	Moclobemide	Fluvoxamine
Trimipramine	Zimelidine		
Butriptyline	Bupropion		
Protriptyline			
Dothiepin			

Tricyclic antidepressants (TCAs), binding to 5-HT and noradrenaline reuptake transporters prevent the reuptake of these monoamines from synaptic clefts and this blockade leads to the accumulation of 5-HT and noradrenaline in synaptic clefts [82].

Monoamine oxidase inhibitors (MAOIs) were the first drugs to be introduced clinically as ADs. Monoamine oxidase is an enzyme involved in the metabolism of 5-HT and noradrenaline (monoamine oxidase A), and dopamine (monoamine oxidase B). MAOIs prevent monoamine degradation [82].

The mechanism(s) of action of mono-, bi-, tetra- and heterocyclic ADs is (are) unknown. The tetracyclic derivatives block presynaptic $\alpha 2$ receptors producing an increase in noradrenaline release [82].

Selective serotonin reuptake inhibitors (SSRIs) are currently the most commonly prescribed ADs. SSRIs restore the levels of 5-HT in synaptic clefts of neurons by binding at 5-HT reuptake transporters, preventing the reuptake and subsequent degradation of 5-HT. In addition to showing selectivity with respect to 5-HT over noradrenaline uptake inhibition, they are as efficacious as TCAs, but devoid of anticholinergic side effects [82].

Episodes of epileptic seizures were observed during treatment with almost all ADs, including trazodone, lithium, and SSRIs (fluoxetine, citalopram, fluvoxamine, paroxetine, and sertraline) [61, 85, 106, 118, 120, 127]. The problem of antidepressant-triggered seizures is a very complex matter because of the varied and complex action of ADs on neuronal excitability.

Some of these drugs (mainly TCAs) decrease the seizure threshold in humans [7, 8, 21, 51, 65, 113]. This idea was supported by results demonstrating that some TCAs, such as imipramine, amitriptyline, and trimipramine, cause activation of alterations in EEG activity in both, epileptic and non-epileptic patients [23, 57, 62, 97, 104]. Clinical investigations suggest that, in a high percentage of epileptic patients, TCAs induce or increase EEG epileptiform discharges. This action was observed after the administration of high doses of TCAs and also in patients with preexisting EEG alterations. On the other hand, TCAs rarely cause EEG epileptiform discharges in non-epileptic patients, and TCA-induced EEG abnormalities are seldom followed by epileptic seizures in both epileptic and non-epileptic patients. It remains controversial whether the new generation of ADs (i.e. SSRI) also exerts this effect. Some authors have reported proconvulsive action of the SSRI fluoxetine [42, 96], while others reported the opposite action [125]. It is important to distinguish whether the studies examined the effect of acute or chronic treatment. Many of the mechanisms, by which the ADs work are only seen after a prolonged administration and depend on the induction of plastic changes in the central nervous system, especially, in the hippocampus and related areas [70].

Accumulating evidence suggests that maprotiline and amoxapine possess the highest seizure risk, especially at high doses [128], whereas doxepin, trazodone and probably fluvoxamine exhibit the lowest seizure risk [26, 101, 103]. Imipramine and amitriptyline at daily dosages up to 200 mg do not provoke seizures [55].

Ferrero et al. [30] investigated a potential of chronic treatment with fluoxetine to decrease the seizure threshold in two different conditions: in naive rats and in rats exposed to an experimental model of depression, the learned helplessness (LH) paradigm. In naive animals, the authors have reported that chronic treatment with fluoxetine evoked a significant decrease in the convulsive threshold assessed by the response to a subconvulsive dose of pentetrazole. On the contrary, the acute treatment with fluoxetine did not induce any change in this parameter. Besides, in naive animals chronically treated with fluoxetine, a significant increment in the basal glutamate release was observed. In non-treated LH animals, a decrease in the K^+-stimulated glutamate release was observed, but when fluoxetine was administered, no change in the susceptibility and no increment in the glutamate release were found [30].

Some ADs may display anticonvulsant effects, especially when administered at low doses in experimental models of epilepsy and clinical settings [11, 12, 33, 34, 58, 73]. The available data suggest, however, that ADs could have both proconvulsant and anticonvulsant effects [92] and that drug dosage is the most important factor in determining the direction of action.

It is probable that drugs increasing serotonergic transmission have lower convulsant liability or, even, are more anticonvulsant than other ADs [82]. Moreover, it is possible (although not investigated) that depressive epileptic patients have poorer reaction to AEDs because of irregular sleep and/or drug/alcohol abuse [109].

There are investigations suggesting that some ADs may display antiepileptic action in patients with epilepsy [29, 34, 80, 105]. This aspect is less known than that ADs may provoke seizures. Millichap [73], probably was the first who has reported that TCAs have an anticonvulsant effect. Subsequently, Fromm and co-workers [33, 34] have observed the therapeutic

effects of low doses of imipramine against absence and minor motor seizures in a small group of patients. In the latter, double-blind crossover study, the authors have reported a significant reduction in absence and myoclonic-astatic seizures in 5 out of 10 patients during treatment with imipramine, despite discontinuation of AED medication [34]. Another report has suggested a therapeutic effect of clomipramine against absence seizures [112]. An effect against partial seizures has been subsequently reported with doxepin in a retrospective analysis [80], clomipramine [105], and with the more recently available fluoxetine in an unblinded, open-label, add-on study [29]. It is suggested that some TCAs and some SSRIs may exert at certain doses an inhibitory action on neuronal excitability and that the mechanism of this effect might be relevant to the development of antiepileptic action.

The role of depression itself in facilitating seizures is a very interesting problem but not clearly investigated.

Interactions

The effect of drug interactions on the rational treatment of psychiatric patients with epilepsy is important from both pharmacokinetic and pharmacodynamic points of view [71]. It should be remembered that kinetic interactions do not exclude pharmacodynamic interactions, and that both kinds of interactions often coexist in the same patient [88]. Pharmacokinetic interaction often appears less important than pharmacodynamic interaction of drugs and neurotransmitters [107].

Pharmacokinetic interactions can occur during absorption, distribution, biotransformation, and elimination of drugs. Several factors must be considered in evaluating the clinical significance of potential drug interactions [117]. These factors include:

1. nature of each drug's activity at an enzyme site (substrates, inhibitors, or inducers),
2. concentration of inhibitors or inducers at the enzyme site,
3. saturability of the enzyme,
4. presence of active metabolites of the substrates,
5. therapeutic window of the substrates,
6. inherent enzyme activity in an individual person,
7. risk level for each individual person to experience adverse effects, and
8. probability of concurrent use (epidemiologic perspective).

In vitro data are important as a starting point for predicting these pharmacokinetic drug interactions.

Because of mutual pharmacokinetic interactions between AEDs and ADs, with consequent marked changes in their plasma concentrations, it remains to be established whether or not plasma AD concentrations that are effective against depression also facilitate seizure initiation.

Most AEDs are potent inducers of hepatic microsomal enzyme (CYP450), and through this mechanism they stimulate elimination of different ADs, including nortriptyline, chlorimipramine, imipramine, desmethylchlorimipramine, protriptyline, and others [15, 45, 74, 75, 86, 90, 100, 119]. This effect may result in decreased plasma drug concentrations, possible reduction in antidepressant efficacy, and possible formation of toxic metabolites displaying convulsant action [2]. The plasma content of mianserin and nomifensine may be low due to accelerated process of desmethylation [77]. VPA can inhibit the metabolism of TCAs [123], and there were observed toxic plasma concentrations of desipramine after discontinuation of VPA [50].

On the other hand, imipramine, nortriptyline, and viloxazine may increase plasma concentrations of PHT, CBZ, and PB [86, 90, 100], and this may lead to drug toxicity, inducing paradoxical activation of seizures [52, 63, 122]. Besides, in case of clomipramine-induced status epilepticus described by DeToledo et al. [24], the elevated plasma concentrations of clomipramine of 342 ng/ml (therapeutic range 70–270 ng/ml), after a daily dose of 75 mg, were probably caused by a concomitant treatment with VPA, which is a well-known inhibitor of hepatic drug metabolism.

The newer SSRIs are not devoid of the liability of interacting with other drugs. They inhibit the CYP2D6 isozyme in the liver and may reduce the elimination of other concomitant drugs [124]. Most likely, this mechanism might have played, at least in part, a role in determining the toxic effects observed during co-medication of fluoxetine with CBZ [25] and PHT [48]. In the study by Keller et al. [56] on the interactions between CBZ and fluoxetine, the plasma concentrations of the SSRI and its active metabolite norfluoxetine remained unaltered for the entire observation period (20 days of treatment).

It is possible that the AED-induced reduction in plasma AD concentrations is responsible for the low

epileptogenic activation *in vivo*, which is conformable to experimental data indicating that low doses of ADs *in vitro* may even be anticonvulsant [67]. Such a "negative interference" implies that patients with depression in the course of epilepsy may need an increase in AD dosages.

Some authors have observed an inhibitory effect of TCAs on the elimination of some AEDs, with a consequent risk of toxicity. PHT concentrations increased in patients treated with nortriptyline [99], and imipramine [87], as well as after administration of nomifensine [77], trazodone [86] and the bicyclic AD viloxazine [88]. Amitriptyline was shown to increase the volume of distribution of VPA in healthy volunteers [91]. Viloxazine interferes with CBZ at various metabolic levels, inhibiting the enzymes that metabolize CBZ. In cases where these two drugs were given together, a 50% increase in plasma CBZ concentrations and a 16% increase in CBZ-10,11-epoxide up to toxic values were observed in some patients [89]. Similar interference of enzymatic inhibition was described for PHT [88]. In the case of interaction between viloxazine and oxcarbazepine (the 10-keto analogue of CBZ), the AD had a modest inhibitory effect on the conversion of hydroxycarbazepine to transdiole, with a 15% increase in plasma of the former [89]. Also, pharmacokinetic interactions have been observed for acute fluoxetine and PB or CBZ or chronic fluoxetine and CBZ, PB, PHT, or VPA in mice – in all these cases brain concentrations of AEDs were significantly elevated [11, 12].

Among the new SSRIs, fluoxetine has been used as an anticonvulsant both in experimental animals [60, 94] and humans [29, 38]. Besides, fluoxetine has been shown either to increase plasma CBZ concentrations [40, 84] or not to modify them [56, 115, 116]. In one case, the fluoxetine-CBZ combination produced a Parkinson-like syndrome [36]. In patients with epilepsy and depression, administration of fluoxetine and CBZ has caused the rise in CBZ-10,11-epoxide plasma concentrations [37]. In a single case, fluoxetine also increased plasma PHT [22, 48, 131] and VPA levels up to toxic values [18]. Moreover, plasma CBZ levels were increased [32] or unaffected [115] by fluvoxamine. In the latter study, CBZ-10,11-epoxide concentrations were also unchanged. Sertraline has a lesser effect on increasing AED levels than fluvoxamine or fluoxetine [71]. On the other hand, paroxetine does not influence CBZ, VPA and PHT metabolism [1].

Conclusions

Mood disorders are an important problem in people with epilepsy because they are often undiagnosed and incorrectly treated. Moreover, depressed epileptic patients generally display more severe seizure activity and greater problems with seizure recovery [17, 47]. Precise diagnosis and effective therapy are very important because of a high suicide rate amongst patients with epilepsy [3, 95]. When considering treatment, one must take into account the positive effects of AEDs, the use of safer ADs at appropriate dosages, the potential for drug interactions, and the importance of adequate maintenance therapy.

Although ADs have the potential to lower the seizure threshold and increase seizures, careful drug selection, dosing, and slow titration can minimize this risk, allowing treatment to proceed.

On the other hand, it is well known that PB and complex antiepileptic polytherapies induce depression even at therapeutic plasma concentrations [31, 98].

Because depression is very common in the epileptic population, further research is needed in this field, especially to clarify the effects of ADs on seizure threshold from an experimental point of view. Finally, it is important to identify clearer and safer guidelines of therapeutic management of patients suffering from epilepsy and depression.

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Mood disorder, also known as mood affective disorders, is a group of conditions where a disturbance in the person's mood is the main underlying feature. The classification is in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD). Mood disorders fall into the basic groups of elevated mood, such as mania or hypomania; depressed mood, of which the best-known and most researched is major depressive disorder (MDD) Mental disorders persistent identified in patients with epilepsy as significant personal and affective disorders, especially depressive and anxiety spectrum observed in the interictal period of the disease. Purpose. Study the frequency of nonpsychotic mental disorders in patients with epilepsy; highlight the clinical features of non-psychotic affective disorders and to analyze the relationship of different variants affective disorders with symptoms of pharmacological resistance. Material and methods.Â Interictal mood and personality disorders in temporal lobe epilepsy and juvenile myoclonic epilepsy. J. Neurol. Neurosurg. disorders), personality disorders (DSM-IV axis II disorders), and behavioral problems. Among these, mood disorders are the most frequent psychiatric comorbidity in PWE with a prevalence of depression estimated between 11% and 60% in patients with recurrent seizures [10,11]. Indeed, it is well established that one of every three PWE will experience a depressive disorder in the course of their life, often associated with anxiety symptoms or a full blown anxiety disorder.Â Citation: Alsaadi T, Shahrour TM (2015) Depressive Disorders in Patients with Epilepsy: Underdiagnosed and Appropriately Managed?. Brain Disord Ther 4: 163. doi:10.4172/2168-975X.1000163. Page 2 of 9. Epilepsy is a central nervous system (neurological) disorder in which brain activity becomes abnormal, causing seizures or periods of unusual behavior, sensations, and sometimes loss of awareness. Anyone can develop epilepsy. Epilepsy affects both males and females of all races, ethnic backgrounds and ages. Seizure symptoms can vary widely. Some people with epilepsy simply stare blankly for a few seconds during a seizure, while others repeatedly twitch their arms or legs. Having a single seizure doesn't mean you have epilepsy. At least two unprovoked seizures are generally required for an