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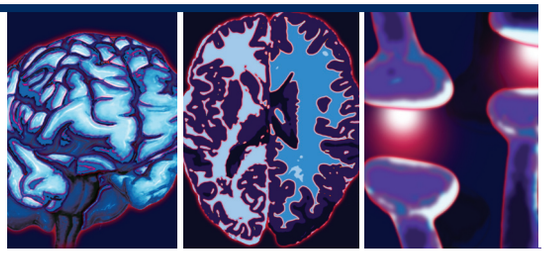

Treatment-emergent psychiatric adverse events of antiepileptic drugs in epilepsy: how can we avoid them?

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Practice points

- Some patients are generally at risk of treatment-emergent psychiatric adverse events (PAEs) whenever a new antiepileptic drug (AED) is introduced.
- Patients with drug-refractory, temporolimbic epilepsy, a previous psychiatric history and/or familial predisposition for psychiatric disturbances need to be followed up regularly for treatment-emergent PAEs when any AED is introduced.
- High dosages and rapid titration schedules significantly increase the likelihood of PAEs.
- Patients with a previous history of episodic behavioral changes or brief psychotic episodes need to be carefully followed up when they are free of seizures.
- When drug removal is indicated, AEDs with mood stabilizing properties (carbamazepine, oxcarbazepine, valproate and lamotrigine) should be carefully and slowly withdrawn in patients with a previous history of a not otherwise specified mood disorder.

SUMMARY Antiepileptic drugs (AEDs) continue to be the basis of epilepsy treatment but benefits of seizure control need to be balanced with their psychotropic potential. In fact, some AEDs are widely used in psychiatric practice in the management of mood and anxiety disorders. However, treatment-emergent psychiatric adverse events of AEDs are more frequently reported in patients with epilepsy than in subjects with psychiatric disorders. Therefore, it can be argued that several factors need to be considered apart from the mechanism of action of the drug. This article discusses available literature regarding clinical and neurobiological variables implicated in the occurrence of psychiatric adverse events during treatment with AEDs in order to operate tailored treatment strategies in patients with epilepsy.

Antiepileptic drugs (AEDs) have several mechanisms of action that are responsible for their activity on seizures [1] in addition to their effects on mood and behavior [2]. In fact, AEDs are widely used outside epilepsy, representing a valid alternative for the treatment of bipolar disorders [3], withdrawal syndromes [4] and anxiety disorders [5]. However, it should be noted that AEDs may have deleterious effects on the mental state of patients with epilepsy [6,7], with

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such effects not being reported in psychiatric populations as frequently as they are in patients with epilepsy [8]. Therefore, it seems evident that variables other than those pertinent to the compound itself (i.e., mechanism of action and kinetics of receptor affinity) may be involved and are probably related to the neurobiology of epilepsy.

In general terms, it is difficult to obtain good data on treatment-emergent psychiatric adverse events (PAEs) of AEDs because it is complex to dissect out the role of the drug among a number of other factors that may affect the patient (e.g., psychosocial reasons, stigmatization, the underlying brain pathology and comorbidities). One possible way would be to withdraw the drug and then readminister it and observe the outcome [9]; however, this would demonstrate causal relationships but not characteristics of patients at risk or the psychopathological features of PAEs. Data on PAEs of AEDs often come from open trials or uncontrolled retrospective studies, which makes it difficult to determine whether the observation was a chance association or a common occurrence. Data from controlled trials also have several limitations because fixed drug doses and specific titration schedules are often required, neither of which are used in clinical practice; the putative compound is tested as add-on with the possible bias of pharmacokinetic and pharmacodynamic interactions; the follow up is usually too short to identify a number of PAEs that may be associated with chronic use. Finally, patients with psychiatric disorders are often excluded, eliminating an important variable. Therefore, it is evident that the assessment of treatment-emergent PAEs of AEDs should consider information available from all possible sources (case series, audit and open observational studies, and controlled clinical trials) to produce an overall view of the problem **(Table 1)**. The interest in PAEs emerged with new AEDs (e.g., vigabatrin, topiramate and levetiracetam) because some of them were associated with psychiatric problems (i.e., vigabatrin) and they represented a interesting model of research [6].

The aim of this article is to discuss available literature on clinical and neurobiological findings associated with treatment-emergent PAEs of AEDs in order to optimize tailored treatment strategies in patients with epilepsy. In fact, the best strategy to treat PAEs is through prevention. Avoiding PAEs maximizes compliance and adherence to treatment, allowing appropriate treatment options according to patients' needs. Articles were identified by searches of Medline/PubMed. Only articles published in English were included. The reference list of relevant articles were hand-searched for additional publications (e.g., book chapters or review papers) if relevant for the discussion.

Variables related to the epilepsy

In the pathogenesis of PAEs, a significant role is played by the limbic structures. Different authors have suggested the association between depression and small hippocampal volumes in both patients with epilepsy [10,11] and without [12]. The fact that limbic system abnormalities may represent a biological vulnerability to PAEs after treatment with AEDs was suggested by our previous studies on topiramate [13] and levetiracetam [14], where we demonstrated that, in both cases, a history of febrile convulsions was associated with PAEs. In fact, febrile convulsions often represent a clinical marker of synaptic reorganization in the limbic system owing to the underlying epileptogenic process [15], and are intimately related to hippocampal sclerosis [16]. In a case–control study, we found that patients with temporal lobe epilepsy and hippocampal sclerosis were more likely to develop depression during therapy with topiramate than patients with temporal lobe epilepsy and normal MRI, matched for age, gender, starting dose and titration schedule of the drug [17]. However, in a more recent study we pointed out that febrile seizures are even more relevant, in association with a rapid titration schedule of the drug, for the development of depression during treatment with topiramate [18]. Our findings are in keeping with a number of data, coming mainly from animal studies, suggesting that functional abnormalities in the limbic system are even more relevant than structural ones, even in normal hippocampi, when febrile seizures occur [19].

Another variable that pertains to the neurobiology of epilepsy is the forced normalization phenomenon. This concept was theorized by Heinrich Landolt who reported a group of patients who had florid psychotic episodes with 'forced normalization' of the EEG [20]. Subsequently, the term 'alternative psychosis' was introduced by Tellenbach [21] for the clinical phenomenon of the reciprocal relationship between abnormal mental states and seizures, which, unlike Landolt's term, did not rely on

Table 1. Treatment-emergent psychiatric adverse events of antiepileptic drugs.

Drugs	Adverse events
Barbiturates	Depression, irritability, aggression, impaired cognition and attention, hyperactivity
Carbamazepine	Irritability, impaired attention
Eslicarbazepine	No data available
Ethosuximide	Behavioral abnormalities, psychosis
Felbamate	Depression, anxiety, irritability
Gabapentin	Behavioral problems in children
Lacosamide	No data available
Lamotrigine	Insomnia, agitation, emotion lability
Levetiracetam	Irritability, emotional lability
Oxcarbazepine	No data available
Phenytoin	Encephalopathy, depression, impaired attention
Pregabalin	Depression
Retigabine	No data available
Tiagabine	Depression, irritability
Topiramate	Depression, psychomotor slowing, psychosis, impaired cognition (word finding and memory)
Valproate	Encephalopathy, depression
Vigabatrin	Depression, aggression, psychosis
Zonisamide	Agitation, depression, psychosis

EEG findings. Since the early observations of Landolt, several authors have documented a number of patients with alternative psychosis [22]. Notably, this phenomenon is not restricted to drug-induced seizure control, but is also probably implicated in *de novo* psychosis following epilepsy surgery and during vagus nerve stimulation [23], suggesting that the mechanism underlying seizure control is more significant than the mechanism of action of the drug. The pathophysiology of forced normalization is still largely unclear. Several authors hypothesized a number of mechanisms that are both electrophysiological and biochemical [24]. One suggestion is that forced normalization reflects ongoing subcortical or mesial temporal epileptic activity with enhanced cortical inhibition [25], which has been referred to as an inhibitory surround in response to ongoing seizures. This explanation argues that ongoing epileptic activity is necessary for the maintenance of inhibition as well as the development of psychosis. Conversely, other authors speculated on the similarities between forced normalization and Todd's paralysis, suggesting that such phenomenon does not represent ongoing epileptic activity but a prolonged response to preceding epileptic activity [26]. Finally, the experimental model of kindling has been advocated as a potential explanation for alternative psychoses of epilepsy [22,27].

Variables related to the patient

It is well known that there are gender differences in the epidemiology of psychiatric manifestations with mood and anxiety disorders being more prevalent in females rather than in males [28]. Furthermore, temperament and character features are determinant for the development of full blown psychopathological states [29]. All these variables need to be taken into account when considering the risk threshold for the development of PAEs in the individual patient **(Box 1)**. The majority of authors agree that the personal psychiatric history of the patient is determinant on the occurrence of PAEs during treatment with AEDs, highlighting the importance of taking a careful psychiatric history before starting a patient on any new AEDs [30,31]. Moreover, the observation that people with a past history of depression tend to develop an affective picture, whilst those who have a past history of psychosis develop a psychotic episode, raises interesting questions regarding the psychotropic effects of AEDs in epilepsy. As pointed out by Trimble, the drugs essentially appear to be driving the underlying constitutional liability of the patients, the direction in which they are driven being given by the past psychiatric profile [32]. Interestingly, a past history of depression has been described as a risk factor for cognitive problems [17,33,34]. Literature on this specific issue is scarce and it is not known

Box 1. Variables implicated in treatment-emergent psychiatric adverse events of antiepileptic drugs.

Direct

Variables related to the drug:
- Potentiation of GABAergic neurotransmission
- Folic acid deficiency
- Rapid titration schedules

Indirect

Variables related to the patient:
- Gender
- Temperament and character features
- Past psychiatric history
- Family psychiatric history

Variables related to the epilepsy:
- Limbic system dysfunction (i.e., history of febrile convulsions and history of status epilepticus)
- Hippocampal sclerosis
- Channels dysfunction
- Forced normalization

whether these findings are drug specific or merely reflect the possibility that anxiety and depression increase the complaint rate, rather than the incidence of cognitive side effects *per se*. Moreover, symptoms such as mental slowing, concentration impairment and memory deficits may represent biological symptoms of depression and this association may reflect a generic detrimental effect of the AED on the mood of patients with epilepsy. Further investigation of this issue is warranted because the mood state of the patient is of relevance in the subjective perception of possible cognitive dysfunction during AED therapy.

Variables related to the drug

In general terms, AEDs could be classified into those that are predominantly sedating and others that are activating. The former are characterized by side effects such as fatigue, cognitive slowing and weight gain and usually determine a potentiation of the GABA inhibitory neurotransmission. The latter have anxiogenic and antidepressant properties and mediate the attenuation of glutamate excitatory neurotransmission [35]. This paradigm is quite straightforward but in patients with epilepsy the scenario is complicated by the epilepsy itself as the occurrence of PAEs are related to the interaction between the drug and the underlying brain disorder.

For a long time, polytherapy has been advocated as a major drug-related determinant for PAEs because of the possibility of interactions and potentiation of mechanisms of action detrimental for the mental state of patients. However, recent data suggest that polytherapy is only indirectly related to PAEs [36]. In fact, patients on polytherapy are usually those with chronic, drug-resistant epileptic syndromes, where psychopathological complications are common.

Biochemical properties of the drug, different from the primary antiseizure mechanism of action, may have a role on the psychotropic potential. There is literature on the association between lowered folic acid levels and mental disturbances in patients with epilepsy [37], although a causal relationship remains to be definitely proven. Folic acid plays a crucial role in several important CNS transmethylation reactions and is linked to monoamine metabolism, suggesting that AEDs affecting folate levels may have an impact on mood [38]. In fact, barbiturates have been linked with the occurrence of depressive symptoms [6] and seem to deplete folate levels [37]; conversely, carbamazepine or lamotrigine, which have well known positive effects on mood [2], have minimal effects on folate levels [39]. Although it seems established that a number of AEDs affect folate levels [40], it has to be stated that there is no evidence for the therapeutic use of folate supplementation in treatment-emergent PAEs in patients with epilepsy.

Finally, the titration schedule of the drug seems to be a major variable influencing tolerability and the occurrence of PAEs. Almost all drugs that require titration need to be slowly titrated in order to reduce the likelihood of adverse effects. Such an effect has been demonstrated for several AEDs such as topiramate [13] and zonisamide [41]. In one of our studies, we demonstrated that the rapid titration of topiramate may have different effects when concomitant risk factors such as febrile seizures or a previous history of depression are present. In fact, a rapid topiramate titration seems to be associated with a fivefold increased risk for depression that raises up to 12.7-fold in the presence of febrile convulsion and 23.3-fold in the presence of a previous history of depression [18].

Conclusion & future perspective

Several factors are implicated in treatment-emergent PAEs caused by AEDs in patients with epilepsy. The risk is likely to be linked to the

severity of the epilepsy syndrome, a rapid titration and high dosages of the drug, and biological vulnerability of the individual subject. In fact, a previous psychiatric history, a familial predisposition and a diagnosis of temporolimbic epilepsy are associated with PAEs. It is important to identify a clinical phenotype at risk of treatment-emergent PAEs in order to inform patients and their families and to make sure that patients are monitored frequently. In this regard, at least one study has reported that treatment-emergent psychiatric effects occurred in approximately 8% of patients with drug-resistant epilepsy, probably via a number of mechanisms, such as forced normalization for example, that are not dependent on the specific drug prescribed [42]. Notably, there are no data regarding PAEs in specific epilepsy populations, such as in elderly patients or women, or in specific epilepsy syndromes (e.g., juvenile myoclonic epilepsy). It seems plausible that subjects with temporal lobe epilepsy might be particularly vulnerable but studies investigating specific liabilities are lacking.

Further studies are needed in order to obtain valuable data on individual drugs and to identify specific problems in different epilepsy syndromes and special populations. Moreover, treatment-emergent PAEs need to be taken into account and carefully explored in Phase III trials. In fact, future drugs and molecules in development will compete for a role in epilepsy treatment not only in terms of efficacy but also, and probably mostly, in terms of tolerability and safety.

Financial & competing interests disclosure

The author has not been paid for the present paper. In the past, the author has received travel grants or consultancy fees, from various pharmaceutical companies involved in the manufacture of antiepileptic drugs, including Novartis, Pfizer, UCB-Pharma and Janssen. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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