Review article

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Antiepileptic drugs and psychopathology of epilepsy: an update

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ABSTRACT – Anti-epileptic drugs (AEDs) continue to be the mainstay of epilepsy treatment, but the benefits of seizure control need to be weighed carefully against possible adverse effects, which can include behavioral problems and psychiatric disorders. In this paper, the associations between AEDs and psychosis, depression and behavioral changes are reviewed. The concept of forced normalization and its clinical counterpart, alternative psychosis, are also discussed. Depression seems to be linked with AEDs potentiating GABAergic neurotransmission in patients with limbic system abnormalities such as hippocampal sclerosis. Psychoses have been described as associated with several of the new AEDs, and they are often seen in a setting in which previously refractory patients suddenly become seizure-free. In general terms, the use of AEDs in monotherapy, adopting slow titration schedules and low doses when possible, can significantly reduce the occurrence of behavioral adverse effects. A previous history of psychiatric disorder or a familial predisposition are important risk factors and should be always considered when choosing the appropriate AED.

Key words: epilepsy, anticonvulsant drugs, depression, psychosis, adverse effects, behavior, mood, AEDs

Psychopathology in epilepsy has a multifactorial etiology and antiepileptic drugs (AEDs) constitute only one of many determinants that are both neurobiological and psychosocial *(table 1)*. It is often difficult to determine which psychopathological manifestations are due specifically to the drug therapy and which may be due to the many other factors affecting the patient. In theoretical terms, a possible way to determine whether a drug is causing an adverse event would be to withdraw the drug, then rechallenge with it and observe the outcome (Mattson 2004); however, such studies have ethical limitations.

The psychotropic potential of AEDs can be divided into those that are positive and those that are negative. Our knowledge about negative psychotropic properties of AEDs is not based on standardized or defined diagnostic criteria. With respect to the older generation of compounds, such as barbiturates, phenytoin or carbamazepine, there are no systematic data, while for the new generation of drugs, there are data from drug trials that are, however, designed to test antiseizure efficacy. Knowledge of the psychopathological phenomenology of psychiatric adverse effects of AEDs as well as the severity, time-course

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Table 1. Causes of psychiatric problems in patients with epilepsy.

(1) Patient-related
- Gender
- Premorbid personality
- Temperament and character features

(2) Epilepsy-related
- Psychological
  - Role of the disease
  - Ongoing social stress and stigma
  - Low expectancy of achievement by family or teacher
- Neurophysiological
  - Low inhibition levels
  - Channels dysfunctions
- Anatomical
  - Hippocampal shrinking
  - Amygdala hypertrophy
  - Head injury
- Brain damage (stroke, head injury, infections)

(3) Anti-epileptic drug-related

and relationship to seizures of such adverse effects remains incomplete.

Ketter *et al*. (1999), reviewing positive and negative psychotropic effects of AEDs, suggested that two categories of drugs could be identified on the basis of their predominant psychotropic profile. *Sedating drugs* are characterized by adverse effects such as fatigue, cognitive slowing, and weight gain; these drugs usually potentiate gamma amino butyric acid (GABA) inhibitory neurotransmission *(table 2)*. On the other hand, there are *activating drugs* with anxiogenic and antidepressant properties that attenuate glutamate excitatory neurotransmission. In the first group, there are drugs such as barbiturates, valproate, gabapentin, tiagabine and vigabatrin, while in the second group there are felbamate and lamotrigine. Topiramate can be considered a molecule with a mixed profile. This paradigm proposed by Ketter is straightforward, but in patients with epilepsy, the epilepsy itself complicates the situation. The psychotropic effects of AEDs are probably related both to *direct* and *indirect* mechanisms *(table 3)*. The former represent the main properties of the drug and can be easily predicted using the theoretical framework suggested by Ketter. On the other hand, the psychopathology associated with an AED may also result from the effect of the drug on the epilepsy itself. Some phenomena, such as forced normalization or post-ictal psychosis, may be the result of AED changes altering the control of the seizures, without being related to a specific drug: any drug that resulted in the same alteration in seizure control in these patients would have resulted in the same psychiatric disorder. Factors such as the severity of the epilepsy or the presence of limbic system abnormalities may be of relevance. A number of good publications have recently reviewed the positive and negative psychotropic potential of AEDs in patients with epilepsy (Gilliam and Santos 2006, Ettinger 2006). In this paper, we aim to review the major psychiatric syndromes described as treatment-emergent adverse effects of AEDs in patients with epilepsy, in a clinical context, discussing possible mechan-

Table 2. Mechanisms of action of anti-epileptic drugs.

	VOC Na blockade	VOC Ca blockade	GABA enhancement	Glutamate antagonism	Other actions
BDZ	-	-	++	-	-
CBZ	++	+ (L)	?	+(NMDA)	+
ETX	-	++(T)	-	-	-
FLB	++	+(L)	+	++(NMDA)	+
GBP	-	++ (N, P/Q)	+?	-	+?
LEV	-	+ (N)	+	?	++
LTG	++	++ (N, P/Q, R, T)	+	++(NMDA, AMPA)	+
OXCBZ	++	+ (N, P)	?	+(NMDA)	+
PGB	-	++ (N, P/Q)	-	-	-
PHB	-	?	+	-	+
PHT	++	?	-	?	+
TGB	-	-	++	-	-
TPM	++	+ (L)	+	++(AMPA)	+
VGB	-	-	++	-	-
VPA	?	+ (T)	+	+(NMDA)	++
ZNM	++	++ (N, P, T)	?	-	+

+ secondary action; ++ primary action; - not described; ? controversial; VOC: voltage opened channel.

Table 3. Mechanisms for psychiatric adverse effects of anti-convulsants in patients with epilepsy.

Direct (drug-related)
- Mechanism of action of the drug (i.e. GABA enhancement or glutamate antagonism)
- Drug toxicity
- Drug withdrawal
- Polytherapy
Indirect (non-drug-related)
• Epilepsy-related
- Forced normalization phenomenon
- Release phenomenon
- Post-ictal syndromes
- Hippocampal sclerosis
• Patient-related
- Psychiatric history
- Familial psychiatric history

isms involved. Relevant references were identified by searches of Medline/PubMed and PsychINFO, using the terms "epilepsy", "depression", "mood", "psychosis", "behavior", "antiepileptic drugs".

The forced normalization phenomenon

Consideration of the concept of forced normalization is essential when discussing the psychiatric adverse effects of AEDs in epilepsy. This concept goes back to the publications of Heinrich Landolt, head of the Swiss Epilepsy Center in Zurich between 1955 and 1971 (Landolt 1958). He reported EEG investigations of patients with epilepsy who had paroxysmal psychiatric disorders, using the newly-introduced EEG, and described a group of patients who had productive psychotic episodes with "forced normalization" of the EEG. In other words, the abnormal EEGs of these patients improved or normalized during the time that they were psychotic. Landolt commented that the introduction of a particular class of drugs, the suximides, led to an increase in the number of cases (Trimble and Schmitz 1998). During the same period, Gibbs (1951) reported intensification of psychiatric disorders in temporal lobe epilepsy when seizures were suppressed with phenacemide, and commented that this could sometimes happen with barbiturates and hydantoins; drug withdrawal could result in reappearance of seizures and resolution of the abnormal mental state (Trimble and Schmitz 1998). Subsequently, Tellenbach (1965) introduced the term "alternative psychosis" for the clinical phenomenon of the reciprocal relationship between abnormal mental states and seizures, which did not, as Landolt's term did, rely on EEG findings.

Since the early observations of Landolt, a number of patients with alternative psychosis have been documented, putting the existence of this phenomenon beyond doubt (Trimble and Schmitz 1998, Krishnamoorthy *et al*. 2002, Seethalakshmi and Krishnamoorthy 2007a). In many of the series described, the precipitation of the abnormal behavioral state or the psychosis has been linked with the prescription of AEDs, but it is important to note that this phenomenon should not be restricted to drug-induced seizure control. It is likely that in patients who develop *de novo* psychosis following epilepsy surgery, forced normalization may play such a role. It is interesting to note, in this context, that a case of an alternative psychosis secondary to vagus nerve stimulation has been reported (Gatzonis *et al*. 2000).

Several psychopathological pictures have been linked to forced normalization, but probably psychosis is the commonest (Krishnamoorthy and Trimble 1999). Wolf (1991) pointed out that several clinical pictures may evolve, not all psychotic, and noted that the development of psychotic symptoms was preceded by premonitory symptoms, especially insomnia, anxiety and social withdrawal. He noted an association with generalized idiopathic epilepsies and the prescription of ethosuximide, again drawing attention to the importance of both generalized seizures and the suximide drugs in the development of these behavioral problems (Wolf and Trimble 1985).

Depression

Mood disorders are the most frequent psychiatric comorbidity in patients with epilepsy, but they often remain unrecognized and untreated (Seethalakshmi and Krishnamoorthy 2007b). The occurrence of depression can have a major impact on the quality of life of patients with epilepsy, even more so than the seizure frequency itself (Gilliam 2003). Among the potential neurobiological and psychosocial determinants, epilepsy variables such as seizure type (temporal lobe epilepsy and partial seizures), severity (the prevalence of depression increases with increased seizure severity) (Harden *et al*. 2007, Turky *et al*. 2008), frequency (either increased or decreased), and AED treatment have been associated with depression (Lambert and Robertson 1999). However, there is some evidence for the following variables being relevant to the association of depressive symptoms with AED therapy: enhanced GABA neurotransmission, folate deficiency, polytherapy, the presence of hippocampal sclerosis, forced normalization and a past history of affective disorders (Mula and Sander 2007).

A number of studies have suggested a link between depression and treatment with barbiturates. Rodin *et al*. (1976) stabilized 45 patients on a combination of phenytoin and either primidone or carbamazepine. After a three-month period, those receiving carbamazepine were switched to primidone and *vice versa*. Over time, patients became clinically more depressed on a regime

of primidone but less so on carbamazepine. In a similarly designed study, Dodrill and Troupin (1977) compared carbamazepine with phenytoin over a four-month period using a double-blind design in which patients were randomly assigned to one of the two drugs. All subjects were evaluated using the Minnesota Multiphasic Personality Inventory, and scores for every clinical scale favored carbamazepine, with statistically significant differences emerging for the scales related to feelings, attitudes and emotions. In patients with epilepsy treated with a monotherapy regime, Andrewes *et al*. (1986) compared 42 newly referred patients with well-controlled epilepsy using a mood adjunctive checklist. They noted blood levels of carbamazepine to be negatively correlated with measures of anxiety, depression and fatigue. Finally, Robertson *et al*. (1987) noted that, in a group of patients on polytherapy presenting with a depressive illness, patients taking barbiturates had been significantly more depressed than patients taking carbamazepine. These results could be explained by an association between the barbiturates and depression, an association between carbamazepine and beneficial effects on depression or both of these factors.

As far as new AEDs are concerned, some have been linked with depression as a treatment-emergent adverse effect *(table 4)*, including vigabatrin (Levinson and Devinsky 1999), tiagabine (Trimble *et al*. 2000) and topiramate (Mula *et al*. 2003a). It is interesting to note that all of these are GABAergic drugs. Mainly because it was the first of the new drugs to be introduced into clinical practice, vigabatrin has been the most studied (Ring *et al*. 1993, Thomas *et al*. 1996). In some patients, the onset of depression was linked with a dramatic control of seizures (a form of forced normalization see Wolf 1984, Trimble and Schmitz 1998), while in others it was unrelated to this. However, in the majority of cases, it appeared to be more common in patients with a history of depression. For example, in the series reported by Thomas *et al*. (1996), 50% of patients reported a history of a mood disorder. It is of interest that some AEDs seem to be more associated with depression than others, especially those with an activity at the benzodiazepine-GABA receptor. In patients with psychiatric disorders without epilepsy, long term treatment with benzodiazepines has been reported as provoking depressive symptoms, (Trimble 1996) and withdrawal can provoke a depressive illness (Olajide and Lader 1984). The link between GABA and depression is not easy to explain, but has been used as further evidence for a GABAergic hypothesis for depression. A number of clinical observations and experimental studies have shown that GABAergic mechanisms are involved in the pathogenesis of depression (Petty 1995).

Although topiramate is usually considered to be an antiepileptic drug with a mixed profile, there is some evidence that its GABAergic properties are prominent. Two healthy volunteer studies have demonstrated that treatment with topiramate was associated with the onset of depression and a significant increase in GABAergic inhibitory neurotransmission (Martin *et al*. 1999, Kuzniecky *et al*. 2002). Although healthy volunteer studies are often criticized for their lack of relevance to the clinical situation, they are important because it is possible to eliminate the confounding variables related to the underlying epileptic processes. A large, post-marketing survey showed that depression is one of the main, treatment-emergent, psychiatric adverse events during topiramate therapy (Mula *et al*. 2003a), and relevant clinical correlates were a rapid titration schedule for the drug, a psychiatric history and, probably, a more severe form of epilepsy as suggested by the association with seizure frequency and the

Table 4. Main effects of anticonvulsants on behaviour in patients with epilepsy.

AEDs	Treatment-emergent behavioral adverse effects
Barbiturates	Depression, irritability, aggression, impaired cognition and attention, hyperactivity
Carbamazepine-Oxcarbazepine	Irritability, impaired attention
Ethosuximide	Behavioral abnormalities, psychosis
Felbamate	Depression, anxiety, irritability
Gabapentin	Behavioral problems in children
Lamotrigine	Insomnia, agitation, emotional lability
Levetiracetam	Irritability, emotional lability
Phenytoin	Encephalopathy, depression, impaired attention
Pregabalin	?
Tiagabine	Depression (non-convulsive status epilepticus), irritability
Topiramate	Depression, psychomotor slowing, psychosis, impaired cognition (word-finding and memory)
Valproate	Encephalopathy, depression
Vigabatrin	Depression, aggression, psychosis,
Zonisamide	Agitation, depression, psychosis

presence of tonic-atonic seizures. Interestingly, co-therapy with lamotrigine was negatively associated, confirming the antidepressant properties of this AED.

In the pathogenesis of AED-induced depressive symptoms, a relevant role is played by the limbic structures (Mula *et al*. 2003b). There is growing evidence in the literature that depression might be linked to small hippocampal volumes, and this association has been described not only in patients with epilepsy (Quiske *et al*. 2000), but also in patients without epilepsy who have a major depressive disorder (Bremner *et al*. 2000, Frodl *et al*. 2002). A case-control study of patients taking topiramate showed that subjects with temporal lobe epilepsy and hippocampal sclerosis were more likely to develop depression than those with temporal lobe epilepsy and a normal MRI, matched for starting dose and titration schedule for topiramate (Mula *et al*. 2003b). Although patients with hippocampal sclerosis tend to be affected by more severe epilepsy, implying that treatment resistance is likely and that polytherapy may be prescribed, the hippocampal sclerosis itself appeared to be the main factor associated with the occurrence of depression (Mula *et al*. 2003b). Folate deficiency is another issue that might be of relevance regarding AEDs and depression. Patients on polytherapy are reported to have low serum, red cell or cerebrospinal fluid folate levels (Reynolds 1976), and this deficit seems to be even greater in patients with epilepsy and psychopathology. It is known that folic acid plays a crucial role in several important central nervous system transmethylation reactions and is linked to monoamine metabolism (Trimble 1996). In this regard, it is worth noting that AEDs with a positive impact on mood and behavior, such as carbamazepine or lamotrigine, have minimal effects on folate levels (Sander and Patsalos 1992). On the contrary, it is established that barbiturates or phenytoin treatment can depress serum, red blood cell, or CSF folate levels in a high proportion of patients (Reynolds 1983).

Psychoses

There is a report demonstrating that, in some cases, AED therapy can be associated with the development of psychosis, with the forced normalization phenomenon being one of the possible causes (Krishnamoorthy and Trimble 1999). Fischer *et al*. (1965) and Roger *et al*. (1968) described episodes of psychoses during treatment with ethosuximide, the EEG often reverting to normal. Another study (Pakalnis *et al*. 1987) described seven patients who had no previous psychiatric histories and whose behavioral problems emerged shortly after starting or altering AED therapy. Their EEGs, abnormal before treatment, normalized during the psychotic episodes. All patients had temporal lobe abnormalities on the EEG, but only two were on suximides.

With regard to the new AEDs, psychoses have been noted, as a potential adverse effect, in several cases, suggesting that this phenomenon is not drug-specific. Psychosis has been described with felbamate (McConnell *et al*. 1996), tiagabine (Trimble *et al*. 2000), topiramate (Mula and Trimble 2003), vigabatrin (Sander *et al*. 1991), zonisamide (Tsuji *et al*. 1993, Kimura 1994 and levetiracetam (Krishnamoorthy *et al*. 2002). Although there is no clear evidence for lamotrigine precipitating psychosis, there are at least some case reports that suggest that this might be a possibility (Brown 1993, Martin *et al*. 1995, Brandt *et al*. 2007). In general terms, the frequency of psychoses during AED treatment seems to be in the region of 1%-2% and all cases described were difficult-to-treat patients undergoing add-on therapy. Psychoses associated with vigabatrin have been the most extensively studied. In the study by Thomas *et al*. (1996), 30% of patients who developed psychosis during therapy with vigabatrin had a history of psychosis and 60% of them became seizure-free. Since these early reports, the clinical significance of vigabatrin-associated behavioral problems has been a matter of controversy, and two meta-analyses have been published (Ferrie *et al*. 1996, Levinson and Devinsky 1999). Analyzing seven placebo-controlled European studies, Ferrie *et al*. (1996) showed an overall occurrence of these complications of 3.4% in the vigabatrin group and 0.6% in the placebo group. Another meta-analysis of American and non-American, double-blind studies demonstrated that there is a significantly increased risk for psychosis, occurring in 2.5% of patients treated with vigabatrin compared to 0.3% in the placebo group (Levinson and Devinsky 1999). Subsequently, other authors investigated in detail the main features of psychopathology emerging from AED treatment and the association with seizure freedom has been replicated with molecules other than ethosuximide or vigabatrin (Mula and Trimble 2003).

Placebo-controlled studies of tiagabine showed that the risk of psychosis was not significantly increased (Sackellares *et al*. 2002). However, the paradoxical provocation of *de novo*, non-convulsive status epilepticus is a specific issue reported by different authors (Schapel and Chadwick 1996) and, in some selected cases, there may be a differential diagnosis with brief ictal psychotic episodes (Trimble 1991). In such an event, EEG investigations are essential.

In general terms, it seems that psychoses with the newer AEDs occurred in early clinical trials, and to some extent were a reflection of two factors. First, a dosing schedule that subsequently appeared to be rapid, or involving dosages that were too high. Second, the populations studied were, in many cases, composed largely of patients with very difficult-to-treat epilepsy and those who had temporal lobe epilepsy, *i.e*. the population of patients that are most susceptible to develop psychoses (Trimble 1991). In other words, certain AEDs appear more likely

to be associated with psychosis, although the latter tends to be seen in those patients who, in any case, are susceptible to developing psychopathology. With the introduction of other powerful drugs in the future, these complications need to be both evaluated and treated.

Behavioral changes

The issue of the relationship between epilepsy and behavior has a long history. One line of thought suggests that behavioral changes in epilepsy are a reflection of a temporal lobe, organic brain syndrome, while other authors suggest that they are more a reflection of social stigma or neurological factors, such as recurrent head injury or perinatal disturbances. In any case, AED medication appears to be another important factor.

One of the first studies investigating this issue was that by Reynolds and Travers (1974), who studied 57 adult outpatients with chronic epilepsy for the presence or absence of behavioral changes or psychiatric disorders, looking at serum AED levels. Patients with behavioral problems had significantly higher levels of both phenobarbitone and phenytoin than those without, irrespective of seizure frequency. Since that time, there have been many studies on the effects of AEDs on cognitive function or mood, but few of them have specifically investigated the issue of changes in behavior. In general terms, drug-induced behavioral problems, including irritability and aggressive behavior, appear to be more frequent with polytherapy and severe epilepsy, where mental retardation or abnormalities in the limbic system might be present (Trimble 1998). For this reason, the trend towards treating patients with monotherapy, particularly this subgroup of more vulnerable patients, would seem important for the patient's overall well-being.

A wide spectrum of behavioral changes has been described with different AEDs. For example, some authors have observed that, in children, a conduct disorder, phenomenologically similar to an attention-deficit hyperactivity disorder, may be provoked by a number of AEDs, the most frequently implicated being the barbiturates (Vining *et al.* 1987, Schmitz 1999). However, there is some debate on this subject, with other authors not demonstrating behavioral problems with phenobarbitone among children (Pal *et al.* 1998, Pal 2006). A similar psychopathological picture (agitation, excitation, hyperkinesias, and aggressive behavior) has been associated with the prescription of other GABAergic drugs, such as vigabatrin, especially in children with learning disabilities (Bhaumik *et al.* 1997, Besag 2004).

Aggressive behavior and irritability have been shown to be two of the main treatment-emergent psychiatric adverse effects during therapy with levetiracetam, occurring in about 5% of patients (White *et al.* 2003). A post-marketing study involving more than 500 patients taking levetiracetam suggested that a subgroup of patients could be biologically vulnerable; a psychiatric history, a history of febrile convulsions and status epilepticus being significant correlates (Mula *et al.* 2003c). Notably, there are several reports suggesting that status epilepticus and febrile convulsions may play a role in the epileptogenic process. The main hypothesis has involved neuronal loss and synaptic reorganization, mainly in the limbic system. These phenomena might explain the biological vulnerability of this subgroup of patients.

The presence of learning disabilities is another important variable that needs to be considered when discussing AED-related behavioral changes in adult patients with epilepsy. Subjects with learning disabilities or mental retardation have a high incidence of all types of epilepsy (Lhatoo and Sander 2001), and the presence of a psychiatric comorbidity in this special population, represents an important variable complicating the management. An audit study conducted in a tertiary referral epilepsy center described aggressive behavior as one of the main treatment-emergent, psychiatric adverse effects in patients with learning disabilities and epilepsy taking levetiracetam (Mula *et al.* 2004). Comparing patients with and without psychopathology, a significant association with the same variables previously described in the general population of patients with epilepsy was found, namely a psychiatric history, and a history of febrile convulsions or status epilepticus. However, the prevalence of psychopathology (about 7%) was similar to that described in previous clinical studies involving a general population of patients with epilepsy, suggesting that patients with learning disabilities are not generally more prone to developing psychopathology with levetiracetam, the baseline mental state of the patient and the presence of some abnormalities in the limbic system being the more relevant risk factors.

In clinical practice, it is sometimes difficult to recognize potential psychiatric adverse effects of AEDs in such populations because patients with learning disabilities may be unable to express what they feel, and changes in behavior can be all that is apparent. In general terms, bizarre behavior or the development of suspiciousness or social withdrawal (especially in institutionalized patients) may give some clues to the epileptologist about the occurrence of psychiatric adverse effects of AEDs. Therefore, the clinical evaluation of the mental state is of great value in this special population of patients when choosing the appropriate AED. Finally, if patients who have been very disabled by frequent seizures over a long period of time suddenly become seizure-free and alert, their behavior may become difficult to manage. This condition is also known as the "release phenomenon" (Besag 2004) and can occur with several AEDs that are effective in controlling seizures with a positive impact on alertness and cognition. In this case, the conclusion should not be that the drug has caused the behavioral disturbance, but that the patient may not know how to express his or her new-found ability in an acceptable way. In such circumstances, skilled behavioral input

Table 5. Variables involved in AEDs-related psychopathology.

	VGB (Thomas *et al*. 1996)	TPM (Mula *et al.* 2003a)	LEV (Mula *et al*. 2003c)	TPM-LEV (Mula *et al*. 2007)
History of febrile convulsions	?	+	+	+
History of status epilepticus	?	+	?	?
Previous psychiatric history	+	+	+	+
Family history of epilepsy	?	+	?	?
Family psychiatric history	?	+	?	+
Seizure-freedom	+	+	+/-	+

can resolve the problem, whereas withdrawal of the AED might return the patient to a disabled state as a result of the frequent seizures.

Conclusion

The most commonly-reported, psychiatric adverse effects of AEDs are non-specific behavioral problems. Among specific psychiatric diagnoses, depression is the most commonly reported. Psychosis is much less frequent. However, one of the major shortcomings of the literature is the failure of most studies to state what behavioral measures or diagnostic criteria have been used. Several factors are implicated and the risk is likely to be linked to the severity of epilepsy, polytherapy, rapid titration and high dosages of the drugs. It is important to identify clinical phenotypes more at risk of developing psychopathology in order to inform patients and their families, and to ensure that these patients are monitored frequently. In this regard, at least one study has reported that treatment-emergent, psychiatric effects occur in about 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 (Mula *et al*. 2007). In general terms, a psychiatric history, familial predisposition, and a diagnosis of temporolimbic epilepsy are associated with an increased risk of psychopathology *(table 5)*. Hippocampal sclerosis is associated with a higher risk of depressive symptoms such as depressed mood and mental slowing. In patients with a history of psychosis, abrupt control of seizures with an AED should probably be avoided so as to reduce the risk of alternative psychosis; if a psychosis does occur, this can usually be managed by reduction or discontinuation of the relevant AED. In clinical practice, if a patient presents with depression, the possibility that this has been precipitated by anti-epileptic medication should be considered and the treatment should be reviewed. In particular, polytherapy should be avoided in such patients. Consideration may be given to prescribing an AED that is more likely to be associated with an improvement in depression, such as carbamazepine or lamotrigine.

There is increasing evidence that good clinical management can decrease the risk of psychiatric adverse effects of AEDs: knowing which drugs are most likely to be implicated, starting with low doses and escalating slowly, and identifying those patients who will require close monitoring because of clinical risk factors, including a history of psychiatric disorders, febrile seizures or hippocampal sclerosis, should decrease the occurrence of such adverse effects in the future *(table 6)*. □

Table 6. Treatment considerations in epilepsy with psychiatric comorbidity.

Co-morbidity	Avoid	Consider
Depression	Barbiturates, VGB, TGB, TPM	LTG
Anxiety	LTG, FBM, LEV	BZD, GBP, PGB
Psychosis	VGB, TPM, ESM	LEV

BZD: benzodiazepines; ESM: ethosuximide; FBM: felbamate; GBP: gabapentin; LEV: levetiracetam; LTG: lamotrigine; TGB: tiagabine; TPM: topiramate; VGB: vigabatrin.

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