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Negative Effects of Antiepileptic Drugs on Mood in Patients with Epilepsy

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Abstract

With the introduction of several new antiepileptic drugs into clinical practice, renewed attention has been focussed on treatment-emergent adverse effects, including mood disorders. There are several possible causes of psychiatric disor-

ders in patients with epilepsy, including antiepileptic drugs, and it is often difficult to determine whether psychopathological manifestations, especially depressive symptoms, are due to drug therapy or to multiple other factors. Assessment of the negative effects of antiepileptic drugs on mood should always consider all potential factors. Case series, audits and open observational studies can identify psychopathological features, case-control studies are useful for identifying the endophenotypes of patients at risk of adverse effects on mood, and controlled clinical trials give good estimates of incidence of such effects, adjusted for the spontaneous occurrence of symptoms.

The barbiturates, vigabatrin and topiramate show greater associations with the occurrence of depressive symptoms than other antiepileptic drugs, presenting in up to 10% of all patients, but even more so in susceptible patients. Data on zonisamide are scarce but it seems that mood disorders may occur in approximately 7% of patients who are receiving high dosages of this drug. In most cases, the use of monotherapy, with slow titration schedules, can significantly reduce the incidence of mood disorders. Tiagabine, levetiracetam and felbamate present an intermediate risk, with prevalence of depression of about 4% or lower. Phenytoin, ethosuximide, carbamazepine, oxcarbazepine, gabapentin, sodium valproate, pregabalin and lamotrigine are all associated with low risks for depression (<1%), and several of these antiepileptic drugs seem to have a positive effect on mood. Antiepileptic drugs can negatively affect mood and behaviour by different mechanisms: potentiation of GABA neurotransmission, folate deficiency, pharmacodynamic interactions with other antiepileptic drugs in polytherapy regimens, forced normalisation.

Individuals with a personal or family history of depression should be carefully followed after initiation of therapy with a new antiepileptic drug, especially if structural brain abnormalities such as hippocampal sclerosis are present.

The association between psychopathology and antiepileptic drug therapy has long been recognised. In the early 1900s, Turner described sedation, memory impairment, and cognitive and affective blunting as adverse effects of bromides.[1] However, systematic evaluation of the effect of antiepileptic drugs on mood and behaviour has taken place only more recently.

It is often difficult to determine which psychopathological manifestations are due specifically to the drug therapy and which may be due to multiple other factors affecting the patient. Psychiatric disorders in epilepsy often have a multifactorial origin (e.g. psychosocial reasons, stigmatisation, the underlying brain pathology), making epidemiological data about the incidence and risk factors difficult to interpret;[2] antiepileptic drugs constitute only one of many putative causes. One possible way to determine whether a drug is causing an adverse event is to withdraw the drug and then rechallenge with it and observe the outcome.[3] However, rechallenging with the drug that has caused an adverse effect should be taken very seriously and the patient should be closely monitored. These studies are useful in assessing causal relationships but they do not provide information about the characteristics of patients at risk or the psychopathological features, which are usually identified by audits and case series.

Putative associations of psychiatric adverse effects with antiepileptic drugs are often based on information from open trials or uncontrolled retrospective studies, and therefore it is difficult to determine whether the observation was a chance associa-

tion or a common occurrence. The best way to assess the incidence of psychiatric disturbances associated with antiepileptic drug therapy, therefore, might be to review data from controlled clinical trials; however, these trials also have several limitations. Clinical trials often test add-on drugs, and thus any psychotropic effect could be attributable either to a pharmacodynamic interaction between drugs or to a pharmacokinetic interaction producing active metabolites. Moreover, clinical trials often require fixed drug doses and specific titration schedules, neither of which is often used in clinical practice. Patients with psychiatric disorders are often excluded, eliminating an important variable. Finally, patients are followed for short time periods and evaluations are conducted too soon to detect the occurrence of effects that might appear later. It is evident that the assessment of negative effects of antiepileptic drugs on mood and behaviour should consider information available from all possible sources (case series, audits and observational studies, controlled clinical trials) to produce an overall view of the problem.

Here we aim to review available literature on the negative effects of antiepileptic drugs on mood in patients with epilepsy. We focused on the major adverse mood effect, namely depression, without considering other affective symptoms such as anxiety, nervousness, emotional lability or aggressiveness. Each antiepileptic drug was appraised, paying attention to data published in international peer-reviewed journals included in Index Medicus; the degree of documentation varies from open studies or case series to controlled clinical trials. We did not review abstracts, posters or oral communications, even if presented during major international congresses, and we concentrated on peer-reviewed literature. References were identified by searches of Medline/PubMed and PsychINFO using the terms 'epilepsy', 'depression', 'mood', 'carbamazepine', 'oxcarbazepine', 'phenobarbital/barbiturates', 'phenytoin', 'ethosuximide', 'valproate/valproic acid/divalproex', 'felbamate', 'lamotrigine', 'topiramate', 'vigabatrin', 'tiagabine', 'gabapentin', 'levetiracetam', 'pregabalin' and 'zonisamide' between January 1970 and June 2006. Only papers published in English were reviewed.

1. Older Antiepileptic Drugs

With respect to the older generation of antiepileptic drugs, such as the barbiturates, phenytoin, carbamazepine and sodium valproate, there are no systematic data and knowledge is largely empirical, based on anecdotal reports or clinical observations.

1.1 Barbiturates (Phenobarbital and Primidone)

An association between treatment with barbiturates and the occurrence of depressive symptoms has often been reported. In a crossover study, 45 patients were stabilised on a combination of phenytoin and either primidone or carbamazepine.[4] After a 3-month period those receiving carbamazepine were switched to primidone and vice versa. Over time, patients became more clinically depressed on a regimen of primidone and less so on carbamazepine. Evidence also comes from studies in adolescents with epilepsy who presented to emergency rooms having taken overdoses, showing that eight of nine patients had been treated with barbiturates.[5] Furthermore, patients taking phenobarbital have been shown to have a high prevalence of major depressive disorder (40%), and of suicidal ideation (up to 47%).[6] In a crossover survey of outpatients with epilepsy,[7] the use of primidone was associated with a high risk of depression (odds ratio [OR] 4.08; 95% CI 2.09, 7.98).

However, a multicentre, double-blind study comparing the efficacy and tolerability of primidone, phenobarbital, phenytoin and carbamazepine in 622 patients did not show statistically significant differences between barbiturates and the other classic antiepileptic drugs in terms of negative effects on mood.[8] In this study, patients were followed up for 3 months, but it seems that mood changes become apparent during long-term treatment of at least 1 year.[9] Thus, patients with a long history of barbiturate therapy are likely to become depressed, especially if they are receiving polytherapy and have a

personal or family history of an affective disorder.[10]

1.2 Phenytoin

Phenytoin has been shown to impair motor speed, concentration and memory in a dose-dependent manner[11] but negative effects on mood seem to be rare. It may provoke behavioural problems other than depression, such as schizophrenia-like psychosis, at high serum levels and in the context of a toxic syndrome characterised by sedation, cerebellar ataxia, ophthalmoparesis and paradoxical seizures.[12]

1.3 Ethosuximide

Ethosuximide has been linked to psychosis rather than to mood disorders,[12] typically following the cessation of seizures and in association with a normalisation of the EEG; this phenomenon is known as 'forced normalisation'.[13]

1.4 Carbamazepine

The occurrence of depression seems to be very rare in people treated with carbamazepine (<1%), a drug that has, on the contrary, demonstrated mood-stabilising properties in psychiatric patients.[14] Carbamazepine was compared with phenytoin over a 4-month period using a double-blind, crossover design in which patients were randomly assigned to one of the two drugs.[15] All patients were evaluated using the Minnesota Multiphasic Personality Inventory, and scores for every clinical scale favoured carbamazepine, with statistically significant differences emerging for the scales related to feelings, attitudes and emotions. As part of a large study to evaluate the effects of rationalisation of polytherapy, 15 patients had one or all antiepileptic drugs switched to carbamazepine,[16] while a control group had no changes to their drug regimen. All were followed over a 6-month period using standard rating scales to assess mood. Patients who were switched to carbamazepine rated themselves as less anxious and livelier during the follow-up period. Patients were then divided into those who had high and those who had low initial pre-change depression scores. Those with higher scores showed a significant improvement after the change to carbamazepine. In another study 42 patients with epilepsy that was well controlled with carbamazepine monotherapy were evaluated using a mood adjunctive checklist.[17] Blood levels of carbamazepine were negatively correlated with measures of anxiety, depression and fatigue.

All these data clearly suggest that carbamazepine has a positive influence on the mood of patients with epilepsy beyond its antiseizure effect, but the applicability of these data to therapeutic situations is uncertain because of the lack of controlled studies specifically designed to assess positive psychotropic effects of carbamazepine in epilepsy. Interestingly, a case report of mania induced by carbamazepine has been reported;[18] the authors suggested a possible paradoxical effect due to the chemical similarities between carbamazepine and tricyclic antidepressants. However, the relationship between antiepileptic drugs, mania and epilepsy is complex and manic symptoms, although rare, have been reported with almost all the available antiepileptic drugs.[19]

1.5 Sodium Valproate

Sodium valproate is well known as a mood stabiliser and is widely used in patients with primary psychiatric disorders, as well as those with epilepsy.[14] Moreover, this treatment possibly has effects on behavioural problems associated with affective lability, aggression, and impulsivity across a range of different clinical contexts.[20] The incidence of negative effects on mood in patients with epilepsy is negligible.

2. Newer Antiepileptic Drugs

As far as newer antiepileptic drugs are concerned, the majority of data come from drug trials. In these studies, behavioural manifestations are not always systematically reported, and this may lead to extrapolations which may be difficult to interpret.

2.1 Vigabatrin

The clinical use of vigabatrin is limited because of negative effects on visual fields. However, it was

one of the first of the newer antiepileptic drugs to be introduced into clinical practice, and so has been the most studied with regard to its effects on behaviour. Shortly after early reports of psychiatric problems,[21,22] their clinical significance became a matter of controversy. A meta-analysis of severe behavioural reactions leading to drug discontinuation in seven European placebo-controlled studies showed remarkably different prevalence rates, ranging between 1% and 12%.[23] This variability suggests that either the risk is not homogeneous in all patient groups or the threshold to report psychiatric adverse effects is not the same among different investigators.

More definite conclusions came from a meta-analysis of double-blind studies that demonstrated a significantly increased prevalence of depression, occurring in 12.1% of treated patients in contrast to 3.5% in the placebo group.[24] However, in monotherapy trials, prevalence seems to be lower and in the region of 5%.[25] Case series of patients with psychiatric disorders associated with vigabatrin therapy made some interesting points. In some cases the onset of depression was linked with a dramatic control of seizures,[21] while in others it was unrelated to this; in the majority of cases, it appeared to be more common in patients with a past history of depression.[26]

2.2 Oxcarbazepine

Oxcarbazepine has been available in some countries for many years. There is extensive experience with this drug in Scandinavia, and it is now widely marketed. The profile of adverse and beneficial effects appears similar to that of carbamazepine,[14] but information about the effects on mood in patients with epilepsy is very limited. Oxcarbazepine may be of value as a mood stabiliser in patients with psychiatric disorders, but there are fewer data available on the use of this drug in such indications than for sodium valproate and carbamazepine.[14]

2.3 Lamotrigine

During clinical trials in the development of lamotrigine it was observed that the drug had antidepressant properties. The cumulative results of studies so far provide evidence that lamotrigine is effective for the management of bipolar depression.[14] CNS adverse effects are often mild and do not usually require drug withdrawal, and they seem to reduce over time. In the analysis of adverse events leading to withdrawal of lamotrigine in 664 patients (included in 27 open-label trials and four randomised, double-blind, placebo-controlled, crossover studies), <1% of patients had to discontinue lamotrigine for any CNS adverse event.[27] This has been confirmed by a meta-analysis of published and unpublished randomised, controlled trials of add-on treatment.[28] Therefore, it can confidently be stated that severe psychiatric complications with lamotrigine are rare events.

The issue of possible detrimental effects on the behaviour of learning-disabled patients with epilepsy is, however, a matter of controversy. Some have reported problems such as aggression,[29] while others have suggested behaviour-enhancing properties independent of the antiseizure effects of the drug.[30] It has been stated that if patients who have been disabled by frequent seizures suddenly become seizure-free without experiencing sedative effects, the consequence may be an increased propensity to misbehave.[31] This condition is known as the 'release phenomenon' and can occur with any antiepileptic drugs that are effective in controlling seizures and have positive effects on cognition, being less sedative. The conclusion should not be that the drug has caused the behavioural disturbance, and the required management approach should be intensive input from medical professionals.

2.4 Felbamate

Felbamate is usually considered a psycho-activating drug and should not have a negative effect on mood. In monotherapy trials, insomnia, nervousness and depression have been reported in <4% of patients.[32] In children these adverse effects are slightly more common (5.5%), especially when felbamate is used as adjunctive therapy, but the problems are severe in <1% of patients.[32] However, the use of

felbamate is limited by serious haematological and hepatic toxicity.[32]

2.5 Gabapentin

Controlled studies of gabapentin have not suggested significant negative effects on mood. Conversely, gabapentin seems to have anxiolytic properties.[14] Some authors have reported isolated cases of behavioural problems such as aggressiveness and hyperactivity in children with severe learning disabilities.[33-35] It is important to underline that all patients presented in these studies were children with learning disabilities, chronic epilepsy, severe encephalopathy, attention deficit hyperactivity disorder and often multiple psychiatric comorbidities. Therefore, there are no conclusive data about a possible detrimental effect of gabapentin in this particular population of patients with epilepsy.

2.6 Tiagabine

The incidence of serious psychiatric adverse events such as psychosis is not significantly increased with tiagabine.[36] However, data from five multicentre, double-blind, randomised, controlled add-on studies suggest that mood disorders occur in 3% of people in the groups taking tiagabine (compared with 1% in the placebo groups).[37-41] Symptoms are usually mild to moderate, occur during titration and resolve spontaneously. Case series of tiagabine-induced psychiatric problems suggest that the patient's previous psychiatric history plays a role.[42] The percentage affected may be lower when tiagabine is used in monotherapy or in patients without a history of mood disorders.

2.7 Topiramate

Topiramate is an effective antiepileptic drug but it is also associated with a high rate of reported adverse effects, especially on cognition.[43] It is known from a study in healthy volunteers that topiramate treatment is associated with the occurrence of depression.[44] In controlled clinical trials, mood effects have not been systematically reported because some symptoms were grouped according to different international codes of clinical information (e.g. Coding Symbols for a Thesaurus of Adverse Reaction Terms [COSTART], WHO Adverse Reactions Terminology [WHO-ART] and the Medical Dictionary for Regulatory Activities [MedDRA]). However, mood lability has been reported with significantly greater frequency in topiramate than placebo recipients and has been identified in up to 17% of patients.[45-47] The rate of affective symptoms is clearly dose dependent and may in part relate to rapid titration schemes. In a postmarketing study of 431 patients, the prevalence of depressive symptoms was 10.7%,[48] the majority of which were major depressive episodes. However, this rate would probably be much lower if topiramate were given as monotherapy, using slow titration schedules. A slow titration schedule was associated with lower prevalence of psychiatric adverse effects (OR 0.43; 95% CI 0.32, 0.58). Another relevant risk factor was having a history of psychiatric disorders (OR 4.48; 95% CI 2.77, 7.25) and probably a more severe form of epilepsy, as suggested by an association with high seizure frequency and the presence of tonic-atonic seizures. Concurrent therapy with lamotrigine was a significant protective factor (OR 0.39; 95% CI 0.21, 0.69), apparently confirming the antidepressant properties of this antiepileptic drug.

2.8 Levetiracetam

Levetiracetam has a favourable adverse effect profile, and depression was reported in 3.8% of patients in a systematic review of four controlled trials and open studies, being a cause of discontinuation in only 0.4%.[49] The analysis of groups receiving different dosages did not show a clear dose-response relationship. An observational postmarketing study of 517 patients[50] and a case-control study[51] showed a similar prevalence for depression: 2.5% and 2.8%, respectively. The relationship between titration schemes and the occurrence of depression is controversial and it is likely that individual susceptibility is the predominant risk factor. A previous psychiatric history was found to play a major role in the occurrence of depression during levetiracetam treatment, and a general biological vulnerability has been suggested.[50] Data from pa-

Table I. Mechanisms of action of antiepileptic drugs

Drug	Voltage-gated sodium channel blockade	Enhancement of GABA neurotransmission	Potentiation of $GABA_A$-mediated neurotransmission	Inhibition of glutamatergic neurotransmission (receptor subtype)	Voltage-gated calcium channel blockade (channel subtype)	Other actions[a]
Benzodiazepines	–	–	++	–	–	–
Carbamazepine	++	?	–	+ (NMDA)	+ (L)	+
Ethosuximide	–	–	–	–	++ (T)	–
Felbamate	++	+	+	++ (NMDA)	+ (L)	+
Gabapentin		?	–	–	++ (N, P/Q)	?
Levetiracetam	–	?	+	?	+ (N)	++
Lamotrigine	++	+	–	++ (NMDA, AMPA)	++ (N, P/Q, R, T)	+
Oxcarbazepine	++	?	–	+ (NMDA)	+ (N, P)	+
Pregabalin	–	–	–	–	++ (N, P/Q)	–
Barbiturates	–	+	+	–	?	+
Phenytoin	++	–	–	?	?	+
Sodium valproate	?	+	–	+ (NMDA)	+ (T)	++
Tiagabine	–	++	–	–	–	–
Topiramate	++	+	+	++ (AMPA)	+ (L)	+
Vigabatrin	–	++	–	–	–	–
Zonisamide	++	?	–	–	++ (N, P, T)	+

a Carbonic anhydrase inhibition, chloride ion channel complex interaction, modulation of synaptic vesicles.

AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; **+** indicates secondary action; **++** indicates primary action; **–** indicates not the action has not been described; **?** indicates the action is controversial.

tients with epilepsy and learning disabilities suggested that <2% had affective symptoms[52] but it is important to emphasise that the diagnosis of depression in learning-disabled persons is often difficult, with the possibility of underestimation.

2.9 Zonisamide

Zonisamide has been used for many years in Japan and Korea, although experience elsewhere with this drug is currently more limited (studies have been published in English, but ethnic differences limit the applicability of the data). In the only European study and the two US add-on placebo-controlled trials, depression was reported in 7.4% of treated patients compared with 3.0% in the placebo group.[53-55] The effect is likely to be dose dependent, as the prevalence of depression is 0.8% in patients taking <200 mg/day, 1.9% in those receiving 200–400 mg/day and 5.8% in patients receiving >400 mg/day.

2.10 Pregabalin

Pregabalin is a recently marketed antiepileptic drug with a favourable psychotropic profile, which is becoming an important treatment option in anxiety disorders such as social phobia[56] and generalised anxiety disorder.[57] Data on the effect of pregabalin on the mood of patients with epilepsy are lacking. However, analysing the data of three pivotal randomised, double-blind, placebo-controlled trials involving >1000 patients, depressed mood seems to be a very rare event (<1%).[58-60]

3. Mechanisms for the Negative Effects of Antiepileptic Drugs on Mood

Antiepileptic drugs have a number of mechanisms of action likely to be responsible for their antiseizure activity but also for their effects on mood (table I). In a review of the psychotropic effects of antiepileptic drugs, it was suggested that two categories of compounds could be identified on the basis of their predominant psychotropic profile:[61] sedating drugs, which are characterised by adverse ef-

fects such as fatigue, cognitive slowing and weight gain and which usually act on GABA neurotransmission; and activating drugs with anxiogenic and antidepressant properties that attenuate glutamate excitatory neurotransmission. In the first group are drugs such as the barbiturates, sodium valproate, gabapentin, tiagabine and vigabatrin, while in the second group are felbamate and lamotrigine. Topiramate is likely to have a mixed profile. Although this proposed paradigm is straightforward, the situation is more complicated in patients with epilepsy. The psychotropic effects of antiepileptic drugs may be related to direct and indirect mechanisms. The first direct mechanisms represent the main properties of the drug and can be easily predicted using the theoretical framework previously described. At the same time the fact that antiepileptic drug-related psychopathology may also derive from the interaction between the drug and the underlying epileptic process should be considered (table II). In fact, some behavioural side effects of antiepileptic drugs do not seem to be as prominently recognised in psychiatric populations, where they are also widely used. Thus some phenomena, such as forced normalisation or post-ictal psychosis, may be pharmacologically driven but are not related to the antiepileptic drug *per se*; they occur exclusively in patients with epilepsy and are related to other variables such as the severity of the disease[58] or the presence of abnormalities in the limbic system (section 3.3). Furthermore, the concept that the mechanisms underlying the control of seizures are strictly linked with those that determine the control of mood and its polarity is suggested by the occurrence of psychopathological states in association with nonpharmacological seizure treatments such as vagus nerve stimulation and epilepsy surgery.[62] However, some variables concerning depressive symptoms driven by antiepileptic drug therapy appear to be relevant: potentiation of GABA neurotransmission, folate deficiency, pharmacodynamic interactions with other antiepileptic drugs in polytherapy regimes, the presence of hippocampal sclerosis, forced normalisation and a past history of affective disorders.

Table II. Mechanisms for adverse effects on mood of antiepileptic drugs in patients with epilepsy

Mechanism
Direct (drug-related)
Mechanism of action of the drug (e.g. GABA enhancement)
Drug toxicity (e.g. folate deficiency)
Drug withdrawal (e.g. benzodiazepines)
Polytherapy
Indirect
Epilepsy-related
Forced normalisation phenomenon
Release phenomenon
Post-ictal syndromes
Hippocampal sclerosis
Patient-related
Past psychiatric history
Familial psychiatric history

3.1 GABA Enhancement

It is notable that the antiepileptic drugs that are more often associated with depression than others (barbiturates, vigabatrin, tiagabine and topiramate) are those with prominent GABAergic properties. Vigabatrin enhances the pool of cerebral GABA, inhibiting GABA transaminase, while tiagabine prolongs the presence of GABA in the synaptic cleft by inhibiting GABA reuptake.[63] Topiramate appears to have several different mechanisms of action, such as the blockade of voltage-dependent sodium channels and L-type calcium channels, the inhibition of the carbonic anhydrase enzyme and an antagonistic effect at the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainite glutamate receptors.[62] However, the psychotropic properties of topiramate may relate to an increase in brain GABA levels following topiramate and a modulatory action at the non-benzodiazepine recognition site of the GABA-A receptor complex.[64] A neuroimaging study performed in healthy volunteers demonstrated that treatment with topiramate is associated with significant augmentation of GABAergic inhibitory neurotransmission.[65] In psychiatric practice, it is known that benzodiazepines can provoke depressive symptoms, and that withdrawal can provoke depressive illnesses.[66] Furthermore, alterations in cerebrospinal fluid (CSF) GABA levels have been reported in patients with major depressive disor-

ders.[67] A number of clinical observations and experimental studies have shown that GABAergic mechanisms are involved in the pathogenesis of depression.[68] The evidence is not easy to explain, but is in keeping with the observation that potentiation of GABA neurotransmission in patients with epilepsy may be detrimental to mood.

3.2 Polytherapy and Folate Deficiency

It is well known that psychiatric complications of antiepileptic drugs may more often stem from the use of polytherapy than from the effects of any individual drug.[69] Patients receiving polytherapy are usually those with chronic, drug-resistant epileptic syndromes, in whom psychopathological complications are common. However, it is important to realise that these psychiatric syndromes may not occur with the same frequency when patients are treated with monotherapy, as suggested by the monotherapy trials so far published in which psychiatric problems have been less frequently reported.

Phenobarbital, phenytoin and primidone have been reported result in low serum, red cell or CSF folate levels, especially when used in polytherapy regimens.[70] An association between lowered folate levels and mental disturbances in patients with epilepsy appears firmly established,[71] although a causal relationship remains to be definitely proven. It is known that folic acid plays a crucial role in several important CNS transmethylation reactions and is linked to monoamine metabolism.[72] Although no clear association with any particular psychiatric disorder has been shown, Shorvon et al.[73] reported that depression was the most common mental disturbance associated with folate deficiency and that it occurred in 50% of folate-deficient patients, compared with 20% of those with vitamin B12 deficiency, in a sample of patients without epilepsy presenting to haematologists or general physicians. Moreover, antiepileptic drugs with a positive effect on mood, such as carbamazepine or lamotrigine, have minimal effects on folate levels.[74,75] Nevertheless, there is no evidence for the therapeutic use of folate supplementation, which can have adverse consequences (e.g. stomach problems or skin reactions at very high doses, or interactions with antibacterials such as tetracycline) in some individuals, although most patients are unaffected.[76]

3.3 Hippocampal Sclerosis

In the pathogenesis of antiepileptic drug-induced depressive symptoms, a role is played by the limbic structures. There is growing evidence in the literature that depression may be linked to small hippocampal volume, and this association has been described in patients with epilepsy,[77] as well as in patients without epilepsy who have major depressive disorders.[78,79] The fact that limbic system abnormalities may represent a biological vulnerability to the negative psychotropic effects of antiepileptic drugs was suggested by our previous studies on topiramate[48] and levetiracetam,[50] in which we showed that, in both cases, a history of febrile convulsions was predictive of psychiatric complications (OR 3.2; 95% CI 1.9, 5.2 for topiramate and OR 2.9; 95% CI 1.4, 5.8 for levetiracetam). It is widely accepted that febrile convulsions represent a clinical marker for the underlying epileptogenic process (the main hypothesis concerns neuronal loss and synaptic reorganisation in the limbic system),[80] and that they are closely associated with hippocampal sclerosis.[81]

In a case-control study, we demonstrated[82] 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 hippocampus upon MRI, matched for age, sex, starting dose and the titration schedule of the drug. Although patients with hippocampal sclerosis are likely to have a more severe form of epilepsy, and patients may experience treatment resistance and be receiving polytherapy, the regression analysis showed that only hippocampal sclerosis, and not the antiepileptic drug regimen, was a predictive factor for depression (OR 2.38; 95% CI 1.10, 5.14). Nevertheless, in a recently published study,[83] we attempted to replicate our findings regarding hippocampal sclerosis and the mood effects of antiepileptic drugs in patients receiving levetiracetam. We compared patients with

temporal lobe epilepsy and hippocampal sclerosis with a control group with temporal lobe epilepsy and normal hippocampus upon MRI, matched for age, sex and titration schedule of the antiepileptic drug. Interestingly, we failed to demonstrate the same association seen with topiramate, suggesting that patients with hippocampal sclerosis may be more likely to develop depression when taking GABAergic antiepileptic drugs such as topiramate, and that the concomitant presence of these two variables (hippocampal sclerosis and GABA enhancement) represents a major determinant in the occurrence of antiepileptic drug-induced depressive symptoms in patients with epilepsy.

3.4 The Forced Normalisation Phenomenon

The concept of forced normalisation goes back to the publications of Heinrich Landolt, who reported a group of patients who had florid psychotic episodes with 'forced normalisation' of the EEG.[84] In other words, the abnormal EEGs of patients improved or normalised during the time that they were psychotic. Subsequently, Tellenbach[85] 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, sufficient numbers of patients with alternative psychosis have been documented by several authors to put the existence of this phenomenon beyond doubt.[86] However, it is important to note that this phenomenon should not be restricted to drug-induced seizure control. It probably plays a role in patients who develop *de novo* psychosis following surgical treatment for epilepsy and a case of an alternative psychosis secondary to vagus nerve stimulation has been published.[87]

Forced normalisation can occasionally be implicated in the occurrence of detrimental effects of antiepileptic drugs on mood. A case series of this phenomenon associated with depression has been reported by Wolf,[88] who described 44 episodes of altered mood in 36 patients with epilepsy, including nine of prepsychotic dysphoria, two of depression and two of dysphoria. Notably, all patients had depressive personalities, a previous history of depression or a family history of depression. However, the role of forced normalisation in mood changes provoked by antiepileptic drugs remains unclear. There are no documented EEG studies and, while a decrease in seizures has been described in association with antiepileptic drug-induced affective disorders,[22,26,89] a complete cessation seems to be unusual.

3.5 Past Psychiatric History

The importance of the psychiatric history of the patient in the occurrence of behavioural adverse effects of antiepileptic drugs has been noted by the majority of authors, emphasising the importance of a psychiatric anamnesis before starting patients on new antiepileptic drugs. Furthermore, the fact that people with a past history of depression tend to develop an affective picture, while those who have a past history of psychosis develop psychotic syndromes, raises interesting questions about the effects of the drugs on the CNS and how they lead to the emergent psychiatric picture. As noted by Trimble et al.,[42] the drugs essentially appear to drive the underlying constitutional lability of the patients, the direction which the changes take being given by the past psychiatric profile.

It is of interest that a past psychiatric history, and a history of depression in particular, was described as a risk factor for cognitive problems during therapy with topiramate.[90] We reported similar findings in patients with cryptogenic focal epilepsy who were receiving topiramate.[82] Literature on this specific subject is scarce and it is not known whether these findings are drug specific or whether they merely reflect the possibility that anxiety and depression increase the complaint rate, rather than the incidence of cognitive adverse effects *per se*. Additionally, symptoms such as mental slowing, impairment of concentration and memory deficits may represent biological symptoms of depression and the association between cognitive problems and topiramate use may reflect a general detrimental effect of topiramate on mood in patients with epilepsy. This

issue deserves further investigation, because the mood of the patient is of relevance in the subjective perception of possible cognitive dysfunction during antiepileptic drug therapy.

4. Conclusion

Among the psychiatric adverse effects of antiepileptic drugs, depression is reported in a significant proportion of patients receiving several different drugs, including barbiturates, vigabatrin and topiramate. Data on adverse mood effects in association with zonisamide are scarce, and tiagabine, levetiracetam and felbamate present an intermediate risk, with a prevalence of depression of about 4% or lower. The other antiepileptic drugs show a low prevalence of depression (<1%) and for some (such as carbamazepine, oxcarbazepine, valproate and lamotrigine) a positive effect on mood has been demonstrated in patients without epilepsy who have primary psychiatric disorders.

The identification of a clinical phenotype associated with a greater risk of developing mood symptoms is important so that clinicians can inform patients and their families and to make sure that the patients are monitored closely. In general terms, the use of antiepileptic drugs in monotherapy, adopting slow titration schedules and low doses when possible, can significantly reduce the incidence of depressive symptoms. A previous history of mood disorders or a familial predisposition are important risk factors and should be always kept in mind when choosing the appropriate antiepileptic drug. A diagnosis of mesial temporal lobe epilepsy seems to be associated with psychopathology in some patients; in particular, hippocampal sclerosis is a risk factor for affective symptoms, such as depressed mood and mental slowing, especially in patients taking antiepileptic drugs that potentiate GABA neurotransmission. In selected cases, the role of forced normalisation or folate deficiency should be considered.

Antiepileptic drugs have a high psychotropic potential in addition to their antiseizure effects that needs to be systematically investigated in patients with epilepsy.

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