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Suicidality and Antiepileptic Drugs
Is there a Link?

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Abstract

The main purpose of the present article is to review the possible risk factors for suicidal behaviour in epilepsy with a special emphasis on the different antiepileptic drugs (AEDs).

Epidemiological data show that, in general, the suicide rate among patients with epilepsy is 5-fold higher than that in the general population, while in temporal lobe epilepsy and complex partial seizures it is approximately 25-fold higher. A certain psychiatric comorbidity may provoke suicidality in patients with epilepsy, and depression and cognitive impairment seem to be the main risk factors for suicidality in epilepsy. In addition, depression and cognitive deterioration in epilepsy may share common neuropsychological mechanisms in terms of hypofrontality. This may cause similar psychopathological signs in both diagnostic categories, including suicidality.

Analysis of the literature has shown that serotonin metabolism disturbances are involved in the pathogenesis of suicidal behaviour irrespective of primary diagnosis. Serotonin disturbances also seem to be a common link between depression, suicidality and even epilepsy itself.

The various AEDs differ not only in their mechanisms of action, but also in influences on cognition and mood in epileptic patients and suicidality, respectively. Until now, only Ketter's hypothesis has been proposed to explain the psychotropic effects of different AEDs, although it does not explain the positive psychotropic effects of some AEDs, such as carbamazepine and oxcarbazepine.

According to this model, all psychotropic effects of AEDs may be the result of effects on the function of two types of receptor functions: γ-aminobutyric acid (GABA) ergic and antiglutamatergic; other possible mechanisms have not been incorporated. Presumably, other neurochemical mechanisms, and a serotonergic mechanism in particular, should also be taken into account when explaining the psychotropic effects of different AEDs.

Based on these data, it has been suggested that AEDs with certain serotonergic properties should reduce the suicidality risk because they exert effects similar to antidepressants (i.e. selective serotonin reuptake inhibitors), whereas AEDs that lack serotonergic mechanisms would not be effective in suicidality prevention. In line with this paradigm, phenobarbital and phenytoin seem to be the only drugs with proven suicidality risk. On the other hand, carbamazepine, oxcarbazepine, valproate and lamotrigine could be regarded as drugs with antisuicidal properties because they all improve cognitive functions and mood in epileptic patients, and possess serotonergic mechanisms of action. The other AEDs, including topiramate, tiagabine, vigabatrin, levetiracetam and zonisamide, all exert negative effects on mood and cognition, although their influence on suicidality has not been proven in evidence-based studies yet. Although zonizamide has serotonergic properties, it exerts negative psychotropic effects, whereas gabapentin is devoid of serotonergic properties but has positive psychotropic effects on mood and cognition.

To more fully explain the positive and negative psychotropic effects and influence on suicidality of AEDs, Ketter's paradigm should be supplemented by an understanding of the serotonergic mechanisms of different AEDs. Further trials are required to prove or refute this model.

The title of this article may seem challenging and rather provocative because it is hard to imagine that some antiepileptic drugs (AEDs) may cause suicide. Suicide is thought to have a multi-factorial origin and every completed suicide should be regarded as a result of a multi-dimensional interaction between different factors. This is the same for suicides in the general population as it is for suicides in certain groups, especially in mentally ill patients.

Although epilepsy is a neurological disease, the condition may lead to a broad palette of psychiatric disorders, including affective and anxiety disorders, psychoses, personality deviations and intelligence deficiency. Each of these disorders may provoke suicide in patients with epilepsy; the suicide risk for each of these disorders is different, although the real degree of each suicidal-risk factor is not strictly determined.

Numerous data have shown that AEDs differ in their modes of action and certain mechanisms *a priori* may interact with other potential risk factors for suicidality, thereby triggering the suicidal behaviour. Ultimately, the final degree of suicidal behaviour and recommendations for suicide prevention can only be described in terms of probabilities.

It should be stressed that completed suicides, attempted suicides and suicide ideation are not the same states and principal differences between them exist, although all these states may be regarded in terms of suicidality within one continuum. Suicidal thoughts without any actual attempts represent one end of the spectrum. Suicidal attempts that have not been completed are thought to be a more severe form of suicidality and fall in the middle of the spectrum. Completed suicides represent the severest form of suicidal behaviour that finalise the aforementioned continuum.

The main purpose of this review is to draw attention to the possible risk factors for suicidal behaviour in epilepsy, with a special emphasis on the different AEDs; however, it should be borne in mind that the role of the AEDs may be an additive rather than a causal factor in a patient's suicide.

A MEDLINE search was conducted for all relevant articles on suicidality under AED treatment and in patients with epilepsy. The search was conducted in March/April 2006. All possible articles relevant to the review topic were analysed and included in the review. The main keywords used included 'epilepsy', 'suicide', 'suicidal risk factors in epilepsy', 'AEDs and suicide', 'personality in epilepsy' and 'serotonin and suicides'. All available journal articles and chapters in monographs (in English and German) relevant to the study topic were also included in the analysis. Additional papers were identified by a hand search of references.

1. Nonpharmacological Risk Factors for Suicidality in Epilepsy

The basic characteristics of epilepsy and psychiatric comorbidity may provoke suicidality in patients with epilepsy. The principal data on this topic are listed in table I. It is noteworthy that generalised and temporal lobe seizures along with psychotic episodes, personality disorders and young age in male patients should be regarded as risk factors for suicidality.[1] Similarly, the role of complex partial seizures as a risk factor for suicidal behaviour has been described.[2-4] Many studies have confirmed that depression and suicidality are more common in patients with complex partial seizures, especially in those with temporal lobe epilepsy.[5-8]

Table I. Nonpharmacological risk factors for suicidality in epilepsy

Variables	Suicidality risk
Simple partial seizures	M↑[9,10]
Complex partial seizures	↑,[1-4] F↓[9,10]
Secondary generalised seizures	M↑[9,10]
Depression	↑,[5-8] F↑[9,10]
Personality disorder	↑,[1] F↑ >M↑,[9,10] ↑[11,12]
Cognitive deterioration	F↑ >M↑,[9,10] ↑[11,12]

F = female; **M** = male; ↑ indicates increase; ↓ indicates decrease.

The sex differences in seizure semiotics also seem to exist in relation to suicidality in epilepsy. Thus, for men, a positive correlation between the suicidality grade and frequency of simple partial seizures and secondary generalised seizures has been demonstrated, which implies an increased risk for suicidality associated with temporal lobe epilepsy in men.[9,10] For women, the inverse correlation between complex partial seizures and suicidality grade was revealed.[9,10] On the other hand, the total sum of all seizures correlated positively with suicidality irrespective of sex.[9]

Depression, personality disorders and cognitive impairment are believed to be the crucial risk factors among psychiatric comorbidity for suicidality in epilepsy,[9-12] although the impact of these disorders on suicidal behaviour should be studied more meticulously.

Concomitant depression is usually the main causal factor in suicidal behaviour in epilepsy, and the incidence of affective disorders in the epileptic population ranges from 11% to 65%.[13-16] Depression may develop during the long-term period of seizure control, which may be explained by reduced excitability of cerebral neurons under continued AED treatment.[2,4,15]

The left-sided foci in temporal lobe epilepsy are thought to be more important in terms of risk factors[17-19] because in such a case the phenomenon of hypofrontality may develop.[20] On the other hand, endogenous (recurrent) depression is believed to be linked with reduced frontal lobe function. Therefore, the hypofrontality may be considered as *conditio sine qua non* for depression development in temporal lobe epilepsy with left-sided foci.[20]

Personality disorders and cognitive impairment in relation to suicidal behaviour in epileptic patients are much less studied than depression. Nevertheless, Steinert and Fröscher[11] and Rösche et al.[12] stressed that personality disorders and cognitive deterioration in epilepsy should also be considered as risk factors for suicidality in the interictal period. These traits concern the constellation of such personality features, which in the 20th century were known under the names 'glishroidia', 'enechetic constitution' or 'ixoid character'.[21] Sex differences were also revealed in suicidality risk factors in relation to these personality traits.[9,10]

2. Common Neuropsychological Basis for Depression and Cognitive Impairment

The cognitive deterioration in epilepsy affects the patient's ability to perform some neuropsychological tests for the assessment of executive functions and working memory. The frontal lobes are believed to be responsible for performing these functions; frontal lobe dysfunction occurs in up to 50% of epilepsy cases and often determines the neurobehavioural complications in epilepsy patients.[22] Principally, in such cases of so-called 'dysexecutive syndrome', symptoms of depression may be present in addition to the reduced executive functions. Indeed approximately half of these patients meet the criteria for major depression.[23]

On the other hand, cognitive deterioration has also been revealed in cases of depression (irrespective of its origin) and depressive patients usually perform much worse than control patients in the neuropsychological tests for attention, vigilance, memory and executive function.[20,23-25] Such poor results are thought to be determined by frontal lobe dysfunction.[22,23] By considering all these data, it can be concluded that depression and cognitive deterioration in epilepsy could share common neuropsychological mechanisms that, in turn, may cause similar psychopathological signs in both diagnostic categories, including suicidality. In other words, both depression and cognitive impairment may represent relatively separate parts of one complex neuropsychological syndrome.

Data from Helmstaedter et al.[26] have confirmed this suggestion. In their study, the inverse correlations between the Beck Depression Inventory (BDI) score and verbal learning, verbal recognition and figural learning for patients with left-lateral temporal lobe epilepsy were obtained, confirming the significance of foci lateralisation for depression development and presumably suicidality. Interestingly, significant correlations between BDI score, right temporal lobe epilepsy (for mesial and lateral) and left-mesial temporal lobe epilepsy were absent. This confirms the significance of left-lateral temporal lobe foci precisely in the development of depression and cognitive impairment in cases of neocortical epilepsy.

On the contrary, in mesial (paleocortical) temporal epilepsy, depression may evolve irrespective of the focus lateralisation.[27] The mean depression score in a study conducted by Quiske et al.[27] was significantly higher in patients with mesial temporal sclerosis, irrespective of mesial temporal sclerosis lateralisation, than in patients with so-called lateral temporal (neocortical) epilepsy. The authors concluded that depression is a good indicator of mesial temporal sclerosis, but not vice versa. However, in such cases, the link between depression and cognitive deterioration is absent.[26] It implies that depression may occur irrespective of the side of the foci in mesial epilepsy, but predominantly in the case of left-sided foci in neocortical epilepsy. In both cases, the risk for suicidality is high enough that it should alarm clinicians.

Along with this conclusion, a suggestion can be made that all AEDs that have the propensity to reduce cognitive function may cause depression and

possibly suicidality if they are used for the treatment of neocortical temporal lobe epilepsy with left-sided foci, but not with right-sided foci. The role of AEDs in the genesis of depression in patients with mesial epilepsy remains unclear and epilepsy itself is much more important in depression development than AEDs, although these suggestions remain entirely speculative and require further study. At present, no systematic studies on this topic have been performed.

3. Neurochemistry of Suicides

A large number of studies have been published within the last three decades that reveal the possible associations between suicides and neurochemical mechanisms.

Dysfunction of serotonin metabolism is thought to be involved not only in the pathogenesis of depression, but also in anxiety, obsessions, aggression and suicidality.[28-37] The data relevant to this topic have revealed the reduced level of 5-hydroxyindolacetic acid (5-HIAA), which is the main metabolite of serotonin, in cerebrospinal fluid of depressed patients with suicidal behaviour. Moreover, a significant correlation was revealed between a decreased level of 5-HIAA in cerebrospinal fluid and aggressive behaviour and suicidal tendencies in patients with personality disorders.[32-35] Moreover, the linear relationship between aggression score in patients with personality disorders and 5-HIAA level in cerebrospinal fluid was found,[32,33] and in the studies by van Praag[36] and van Praag and Plutchik[37] a much more reduced level of 5-HIAA was observed in cases with more severe depression compared with mild cases. Whether the decreased 5-HIAA level in cerebrospinal fluid in patients with depression is a primary or secondary phenomenon (due to the hyperactivity in postsynaptic receptors) remains unclear.[28,36,37]

The data on brain serotonin 5-HT_2 receptor binding in depressed patients have confirmed the protective role of serotonin in suicidal behaviour.[28] The 5-HT_2 receptors are located on the postsynaptic neurons and their maximal density seems to be in the frontal cortex projections of the ascending dorsal raphe nucleus.[28] Based on the experimental observation that the lesioning of serotonergic neurons in the raphe nuclei leads to up-regulation of the postsynaptic 5-HT_2 receptors and decreased imipramine binding presynaptically, Stanley and Mann[38] suggested that if the serotonin hypothesis is operative, then a similar pattern would be found in suicide completers.[39] The authors found that the density of 5-HT_2 receptors was 44% higher in the frontal cortex of suicide victims than in the control group.[28,38] These data were subsequently confirmed in some, but not in all, studies.[28]

Several principal conclusions may be made after these aforementioned findings. First, the study of platelet 5-HT_2 binding is a useful test for the prediction of suicidality, irrespective of the primary psychiatric diagnosis. Secondly, in epileptic patients with a high risk of suicidal behaviour, similar results should be obtained, although such a trial has not been explored yet. Thirdly, possible association might exist between suicidality, platelet 5-HT_2 binding and cognitive deterioration in patients with epilepsy, although again the specific data relevant to this issue are absent. If the third suggestion is true, then simple and robust tests would be useful in predicting suicidality following treatment with individual AEDs.

4. Serotonin Mechanisms in Epilepsy

In addition to the recognised role of serotonin in the genesis of depression, anxiety, obsession and suicidality, evidence exists that implicate its role in epilepsy. The general understanding that serotonin plays a certain role in epilepsy is based as much on evidence from animal models of epilepsy as from clinical observations.[40-46] Thus, in a genetically epilepsy-prone rat model of generalised epilepsy, the serotonin level in the brain,[41] [^{3}H]serotonin uptake by synaptosomes and tryptophan hydroxylase activity are decreased.[42] Furthermore, drugs that facilitate serotonergic transmission inhibit seizure activity in many animal models of epilepsy.[42] Conversely, a reduction of brain serotonin levels leads to an increase in seizure susceptibility in

animal models of epilepsy as well as in humans.[43-45]

However, contradictory data exist indicating that serotonin depletion by use of parachlorophenylalanine protects against experimental atypical absence seizures in rats.[46] Serotonin seems to exert equivocal influence on different types of seizures, and this can in some way explain the contradictory data.

The depletion of serotonin is thought to decrease neurogenesis, whereas the use of antidepressants (mostly selective serotonin reuptake inhibitors [SSRIs]) increases serotonin levels in the brain and thereby facilitates neuroplasticity and neurogenesis in the hippocampus.[40] This can be seen in positron emission tomography (PET) scanning studies, if the tryptophan analogue α-[^{11}C]methyl-L-tryptophan (AMT) is used to measure serotonin synthesis in the human brain.[40]

Principally, decreased hippocampal volume and decreased 5-HT$_{1A}$ binding in the mesiotemporal cortex and in the raphe have also been revealed in patients with depression.[40,47] Serotonergic mechanisms seem to represent the common pathogenetic link between epilepsy, depression and suicidality. The study of Gilliam et al.[48] confirmed this. The authors evaluated epilepsy and depression severity in 62 patients with refractory temporal lobe epilepsy in relation to fluorodeoxyglucose-PET findings. Of these 62 patients, abnormal PET images were observed in 55 patients and normal images were observed in seven patients. The BDI was used for the assessment of the degree of depression. Interestingly, the BDI scores were higher in the group with abnormal PET images than in the group with normal PET results (9.7 ± 8.5 vs 1.8 ± 2.6, respectively; $p < 0.01$). These data help to explain the high frequency of depression in temporal lobe epilepsy and are relevant to the findings on the bidirectional relationship between depression and epilepsy.[49,50] This implies that depression may not only develop after the onset of epilepsy (a widely recognised fact), but may also precede the onset of epilepsy.

Thus, depression and epilepsy in some patients should be regarded as one disease and serotonin seems to be the common link between these two diagnostic categories.

5. Mode of Action of Antiepileptic Drugs (AEDs) and Psychotropic Effects

Assessment of the psychotropic properties of AEDs was seldom the aim of any trial in epileptology. These effects were broadly assessed in the treatment of bipolar and schizoaffective disorders but this goes beyond the scope of present article.

All AEDs have certain differences in their modes of action and in their efficacy in different types of seizures. This requires physicians to select the appropriate AED based on the individual patient's characteristics following the motto 'the right drug for the right patient'; however, the seizure semiotics and adverse events of AEDs are often taken into account while their psychotropic properties, as a rule, are ignored.

The influence of AEDs on suicidal behaviour in patients with epilepsy has not been studied systematically to date and only a few reports exist.[9,10] All available findings in this domain were received after casual observations. These circumstances make it very difficult to present a great vista of issues covering suicidality and AEDs from the point of view of evidence-based medicine. Nonetheless, because of the lack of evidence-based data, these few clinical reports should be included in the final analysis of the problem, although the risk of suicidal behaviour during AED treatment can only be approximately assessed, taking into account the presence of depression and cognitive deterioration developed after the use of a specific AED.

Although the psychotropic properties of AEDs *per se* were seldom evaluated, endeavours were made to create a paradigm that explains the psychotropic effects of these drugs. One of these models, proposed by Ketter et al.,[51] explained the complete range of affective effects of AEDs based upon their neuroreceptor modes of action. According to this paradigm, all psychotropic effects of AEDs may be the result of effects on the function of two types of receptor functions: γ-aminobutyric acid (GABA) ergic and antiglutamatergic. Positive effects on

GABAergic function determines the sedating, anxiolytic and antimanic effects of AEDs, whereas the antiglutamatergic function causes activating, anxiogenic and antidepressive effects. Ketter et al.[51] divided all available AEDs into two groups in relation to their dominant mechanism of action. According to this model, barbiturates, benzodiazepines, valproate, vigabatrin, tiagabin and gabapentin are all drugs with a GABAergic mechanism. On the other hand, felbamate and lamotrigine, in line with the model of Ketter et al.,[51] belong to the group of drugs with an antiglutamatergic mechanism. In addition, topiramate occupies the intermediate position between the aforementioned mechanisms because of its polyvalent mode of action.

The GABAergic functions and consequent sedative effects are needed for the treatment of activated patients with psychomotor excitement, and excited patients benefit from these effects. Conversely, the antiglutamatergic functions and activating effects are desirable for the treatment of depressed and inhibited patients. Moreover, primarily sedated and inhibited patients *a priori* would become worse if they were treated mainly with an AED with the GABAergic mechanism. Conversely, patients with an activated profile at baseline may become worse under treatment with an AED with the antiglutamatergic mechanism.

This model represents an oversimplification of complex psychiatric phenomena in patients with epilepsy and the psychotropic effects of AEDs. However, as some authors argue, it promises a useful approach and a starting point in identifying optimal drugs for specific patients, based on their psychotropic profiles.[20,52] However, the current paradigm unfortunately does not take into account other possible modes of action of AEDs that could also explain the pathogenesis of depression and suicidal behaviour in epilepsy. Several questions remain unanswered regarding this issue.

First, the strict dichotomy of all psychiatric phenomena in epileptic patients into sedation and activation hardly reflects clinical reality and represents the rather oversimplification of complex psychopathological syndromes. This is because the symptoms of depression and anxiety often overlap and in such a case the possibility for comorbidity exist. Principally, in comorbidity of depression and anxiety the maximal risk for suicidality exists.[53] Secondly, Ketter et al.[51] have limited their paradigm to only two modes of action and have not considered the possibility of other mechanisms in depression, anxiety, suicidality and the antidepressant properties of AEDs. Thirdly, the authors have not tried to relate their model with findings on cognitive deterioration (mostly executive function, working memory and verbal fluency) during AED treatment. Obviously, some other mechanisms are also involved in the pathogenesis of epilepsy, depression, anxiety and suicidality, and possibly in the mode of action of some AEDs, and these mechanisms should be elucidated by further studies.

6. AEDs and their Influence on Depression, Cognition and Suicidality

6.1 Phenobarbital

Phenobarbital remains one of the oldest AEDs still widely used for epilepsy treatment all over the world. The low price of phenobarbital and its efficacy against the broad range of seizure types is the main cause of its popularity. Nevertheless, phenobarbital actually represents a single AED that exerts widely recognised adverse effects on cognitive and affective spheres in patients with epilepsy. Cognitive deterioration, depression and suicidality are believed to be the most frequent behavioural adverse effects observed during phenobarbital treatment.[54-63] A majority of studies evaluating the risk of development for undesirable behavioural problems concluded that there was a link between phenobarbital treatment and the incidence of depression, the development of mood disorders and suicidal ideation.[62]

In the study by Brent et al.,[54] the prevalence of major depression in children receiving phenobarbital (n = 15) and carbamazepine (n = 21) was studied. Of the children receiving phenobarbital, 40% were diagnosed with major depressive disorder compared with only 4% of the children receiving

carbamazepine. Interestingly, the frequency of suicidal ideations was 47% vs 4% ($p = 0.005$), respectively. In a study by Kalinin and Polyanskiy,[9] the positive correlation between mean daily dose of phenobarbital and suicidal-severity grade, regardless of the patient's sex, was revealed. In another study by Kalinin and Polyanskiy,[10] the authors showed that the mean daily dose of phenobarbital was included in the discriminant analysis equation for suicidality prediction in women only and, therefore, the final suicidal risk was increased in the female group. The authors concluded that long-term use of phenobarbital could result in a psychotoxic (neurotoxic) effect and consequently in suicidal attempts mostly in females.

Phenobarbital cannot be considered a harmless AED for long-term treatment in patients with epilepsy and numerous data confirm the depressogenic properties and damaging effect of phenobarbital on cognitive functions.[54-63] This could explain the prosuicidal effect of phenobarbital and should warn against broad use of this drug in epileptic patients with depression or cognitive disability.

The folate deficiency caused by phenobarbital is believed to determine the negative psychotropic effects of this AED and to lead to the gradual onset of depression, psychosis and, finally, dementia.[64,65]

6.2 Phenytoin

Phenytoin is the oldest epilepsy medication after phenobarbital and it is still widely used in epileptology because of its excellent anticonvulsant properties and broad-spectrum efficacy. Nevertheless, as a result of its undesirable psychotoxic effects (i.e. sedation, psychomotor slowing, cognitive impairment and depression with suicidality), phenytoin should not be regarded as an ideal AED.[66,67] However, cases of hyperactivity, alterations of emotional state and agitation have been described, although only in higher dose regimens. As with phenobarbital administration, folate deficiency has also been detected in patients treated with phenytoin,[64,65] which may be regarded as a possible common pathogenetic link between phenytoin and depression and suicidality,[68] although this has not been proven in other studies.[62]

Furthermore, the findings on cognitive and mood deterioration as a result of phenytoin treatment are equivocal and the ambiguous data are presented in a review by Parnas et al.[69] The depressogenic effect was observed in two studies: in one study an increase in anxiety level was reported and in the other study a sedating effect was reported.[70,71] In other words, phenytoin produced positive and negative mood effects in an equal number of reports.[16]

Although Aldenkampf et al.[72,73] stressed that the differences in psychotropic properties between phenytoin, carbamazepine and valproate can usually be considered relatively small when these drugs are used within a normal therapeutic range, a certain amount of caution in relation to depression and suicidality should be taken into account in cases of phenytoin prescribing.

6.3 Carbamazepine

Carbamazepine is the main AED used for the treatment of localisation-related forms of epilepsy, and remains the drug of choice for the management of partial seizures (simple and complex partial seizures with and without secondary generalisation). The principal mode of action of carbamazepine is quite similar to that of phenytoin but with less of a 'slowing' effect in the recovery state compared with phenytoin.[73-75]

Another neurochemical mechanism that has not received the necessary attention of clinicians concerns the influence of carbamazepine on serotonin levels in the interstitial space. In experimental animal models, serotonin levels have been reported to increase after carbamazepine treatment at therapeutically relevant doses.[76-78] A serotonin level increase may contribute to the antiepileptic efficacy of carbamazepine by stimulating GABA or by activation of inhibititory serotonin receptors.[79] This effect seems to be similar to those of antidepressants, i.e. SSRIs. Moreover, SSRIs are now regarded as drugs with anticonvulsant and cerebroprotective properties, and their administration is thought to increase neuroplasticity.[80,81]

Based on all these findings, we may conclude that carbamazepine should reduce the risk for depression and suicidality in patients with epilepsy because of its serotonergic mechanisms. Nevertheless, carbamazepine is not an effective antidepressant,[66,67] although it may be useful for treating impulse control disorders, such as borderline personality disorder with aggression.[67,82] Although this diagnosis at first glance is not relevant enough to the topic of current review, it should be remembered that in a person with borderline personality disorder the risk for suicidal behaviour is much higher compared with healthy individuals.[66,82]

Moreover, a number of studies on carbamazepine have revealed an activating 'psychotropic' effect (i.e. improving mood).[83,84] A study by Dodrill and Troupin,[84] revealed the mood-improving effect of carbamazepine in comparison with phenytoin. However, after the authors controlled for the high serum levels of both AEDs, they could not find any difference between the drugs in a reanalysis 14 years later.[85] An opinion exists that the previously described positive psychotropic properties of carbamazepine may not be explained by a directly favourable effect of the drug itself, but rather by the discontinuation of more sedative drugs previously used by the patient, and by improved seizure control.[85]

In contrast to a previous study,[69] some authors, based upon their own experience in psychiatry,[52] regarded carbamazepine as a drug with a "sedating psychotropic profile" used for the treatment of depression and dysphoria. This *a priori* implies an antisuicidal property too. Indeed, in studies by Kalinin and Polyanskiy,[9,10] the inverse correlation between the mean daily dose of carbamazepine and suicidality grade was revealed in the female group and the combined group of patients, but not in the male group. In other words, the antisuicidal property of carbamazepine has been found separately for females, but not for males with epilepsy. The authors interpreted their results in terms of more expressed vulnerability of women with epilepsy for the development of depression in comparison with men. Carbamazepine could reduce the suicide risk as a result of a possible antidepressive, even antidysphoric, effect in epileptic females with depression, but not in males because the probability for depression in women is higher than in men.[9,10]

In summary, carbamazepine remains the drug of choice for the treatment of partial seizures associated with mood disturbances and suicidality because it improves affective symptoms and reduces an amplitude of affective undulations and aggressive behaviour in patients with epilepsy. It has been demonstrated that an inverse correlation between the mean daily dose of carbamazepine and suicidality rate exists.[9,10] Nonetheless, whether there is an association between its blood concentration and suicidality remains unknown. If the inverse correlation between serum carbamazepine concentration and suicidality rate was obtained, this drug could be regarded as an antisuicidal agent and should be used for the purpose of suicide prevention in epileptic patients.

6.4 Oxcarbazepine

Oxcarbazepine is structurally similar to carbamazepine, but the drug has certain advantages, including a nonoxidative metabolic pathway and consequently low induction potential.[86] However, data on the effect of oxcarbazepine on serotonin levels are inconsistent and controversial. Some authors believe that, unlike carbamazepine, oxcarbazepine does not influence interstitial serotonin levels,[78,79] whereas others stress that the serotonin synthesis, turnover and metabolism may be increased by oxcarbazepine.[87] Nevertheless, whether there is any relationship between the neurochemical effects of oxcarbazepine and its influence upon mood and behaviour remains unknown, and a specific study is required to prove or refute this suggestion.

Clinical findings on the efficacy of oxcarbazepine for psychopathology, including mood disorders and suicidality in epileptic patients, are limited and a definite conclusion on its anti- or prosuicidal effect cannot be made. Nevertheless, when oxcarbazepine is used to treat children, observation suggests that the drug is able to improve mood levels to a similar degree as lamotrigine.[88]

The psychotoxic effects (cognitive adverse effects) of oxcarbazepine have not been evaluated systematically to date and contradictory results have been obtained. Thus, in the study by Aikia et al.,[89] the cognitive adverse effects of oxcarbazepine in patients with epilepsy were similar to those seen in patients receiving phenytoin. However, in another study there were no differences between carbamazepine and oxcarbazepine in cognitive testing, and neither AED disturbed memory nor attention in patients with newly diagnosed epilepsy.[90]

In the study by Sabers et al.,[91] the influence of three AEDs (carbamazepine, oxcarbazepine and valproate) on intelligence, learning and memory, verbal span, attention, psychomotor speed and visuospatial construction in patients with newly diagnosed epilepsy was evaluated. The results indicated no deterioration of cognitive function in any treatment modality after treatment within 4 months. In other words, all the compared drugs were quite similar in terms of their favourable influence on cognitive functions.

Interestingly, in another study performed in healthy individuals, oxcarbazepine administered in daily doses of 300mg and 600mg caused a stimulant effect in comparison with placebo.[92] Nevertheless, in patients with epilepsy, oxcarbazepine increased sedation and reduced aptitude on the psychomotor tests (performance, focused attention task, manual writing, alertness) 2–6 hours after administration.[93,94]

In summary, data on the influence of oxcarbazepine on mood and cognitive functions as a whole have demonstrated a favourable drug profile that is comparable with carbamazepine, although the single observation exists that oxcarbazepine exerts deteriorating effects on cognitive function in epileptic patients. Obviously, a definite conclusion cannot be made yet because of the small number of observations. Similarly the influence of oxcarbazepine on suicidality risk cannot be determined because this topic has not yet been adequately studied.

6.5 Valproate

Valproate continues to be regarded as the 'gold standard' in the treatment of all seizure types. Its principal mode of action is the enhancement of GABA functions in the brain.[95] Valproate influences other mediator systems, but this has not received much attention. Nevertheless, it has been reported that valproate enhances extracellular levels of serotonin in the hippocampus and striatum of rodents, and induces a behavioural syndrome in rats known as the 'wet dog shakes', which is regarded as similar to the serotonin syndrome.[68,96] Moreover, in bipolar patients, an ameliorating effect of valproate treatment upon central serotonergic transmission in the L-5-hydroxytryptophan (L-5-HTP) test has been shown.[97] All these data certainly indicate the definite serotonergic action of valproate. However, the correlation between serotonergic effect and anticonvulsant properties of valproate has not been revealed.[97]

The efficacy of valproate in the treatment of bipolar disorder is a well known fact, whereas the findings on its use for the treatment of depression are scarce.[98] Nevertheless, data exist that show the efficacy of valproate in the treatment of depression, particularly with atypical features,[99-101] and in borderline personality disorder with aggressive behaviour.[102-104] Based on these findings, the antisuicidal properties of valproate can be predicted, since suicide is usually attempted by patients with depression or aggressive behaviour.

At present, there are data that demonstrate the antisuicidal properties of valproate in epileptic females, but not in males. For women, an inverse correlation between mean daily dose of valproate and suicidality grade was shown.[9,10]

The psychotoxic effects of valproate treatment (on cognitive function) are thought to be minimal.[105-107] Thus, in the study by Prevey et al.,[107] valproate was compared with carbamazepine for its effects on motor speed and co-ordination, memory, concentration and mental flexibility. No significant differences were obtained between studied AEDs or in the comparison between pretreatment levels and following 6 and 12 months of treatment. Neverthe-

less, subtle cognitive impairment may be revealed in children, particularly if high doses are used.[106]

In conclusion, valproate as a rule does not exert any serious cognitive deterioration if it is used in therapeutically adequate doses in adult epileptic patients. This corresponds with its positive antidepressant effect and antisuicidal properties. In other words, there is a certain similarity between valproate and carbamazepine in terms of their cognitive effects, and antidepressant and antisuicidal properties, despite their differences in structure and mode of action. Similar serotonin-enhancing properties in these two AEDs possibly explain the similar preventive effect against suicidality, although this needs to be demonstrated in a specific study.

6.6 Topiramate

Topiramate is one of the modern AEDs. It has proven efficacy against most seizure types except for absences. In addition, the excellent efficacy of topiramate in cases of so-called 'intractable epilepsies' has also been proven in numerous trials.[108-110]

The polyvalent mechanism of action is thought to determine efficacy of topiramate against the majority of epileptic seizures[111] and, as has been suggested by Ketter et al.,[51] to exert a unique spectrum of positive psychotropic effects. However, topiramate has no effect on serotonergic function. Perhaps, this is one of reasons for the negative psychotropic effects of topiramate, which the model of Ketter et al.[51] did not take into account.

Negative psychotropic effects of topiramate have been observed in several studies. They concern the influence of the drug on cognition and on mood with consequent development of depression, anxiety, psychosis and even suicidality.[72-75,111-116]

The cognitive adverse effects of topiramate include impaired concentration and attention, poorer performance on verbal fluency tests, and emotional lability.[112-114] Interestingly, in patients with partial and generalised epilepsies, topiramate seems to impair performance on the tests on verbal fluency, verbal IQ and list learning with no significant effects on spatial memory, measures of intellect, and list and story recall.[112] In other words, topiramate mainly influences the left hemisphere of the brain and has much less effect on the right hemisphere, although this topic warrants further study.

These kinds of negative psychotropic effects of topiramate do not develop in all patients with epilepsy. Thus, in a study by Mula et al.,[115] depression and cognitive dysfunction were compared in patients with temporal lobe epilepsy with hippocampal sclerosis (n = 70) or cryptogenic epilepsy (n = 128). It was noteworthy that depression and cognitive dysfunction developed in patients with hippocampal sclerosis, but not in patients with cryptogenic temporal epilepsy.

In another study by Mula et al.,[116] the occurrence of febrile seizures in early childhood was proven to be one of the strongest predictors of an adverse psychiatric reaction to topiramate (depression, cognitive deterioration). A history of febrile seizure is regarded as a strong predictor for the future development of mediotemporal epilepsy with hippocampal sclerosis. These findings again confirm the high probability for the occurrence of psychiatric adverse events in topiramate-treated patients with mediotemporal epilepsy. Obviously, hippocampal sclerosis seems to be *conditio sine qua non* for negative psychotropic effects of topiramate. Based upon these findings, it can be speculated that in temporal lobe epilepsy with hippocampal sclerosis, serotonin deficiency plays a central role in the development of depression with consequent possible suicidality.

Several lines of evidence can confirm this suggestion. First, serotonin is recognised as a regulator of neurogenesis in the dentate gyrus.[40,117] Secondly, the depletion of serotonin decreases neurogenesis and neuroplasticity, whereas the administration of an SSRI conversely increases serotonin levels in the hippocampus and facilitates neurogenesis.[40,118] Thirdly, mediotemporal epilepsy with hippocampal sclerosis is characterised by reduced hippocampal volume,[119,120] which is quite similar to that in nonepileptic patients with depression.[40,47,48] It is probable that topiramate cannot reverse depression in mediotemporal epilepsy because of its lack of serotonin-enhancing properties. In such cases,

topiramate seems to play a strictly additive role, whereas the depression itself is caused by hippocampal sclerosis.

Suicidal behaviour during topiramate treatment has been reported in an article by Abraham;[121] however, a single clinical vignette is insufficient evidence on which to base conclusions regarding the drug. Nevertheless, certain caution is needed if cognitive deterioration or depression appears during topiramate administration. To prevent suicidality, topiramate should not be used in patients with temporal lobe epilepsy and hippocampal sclerosis, although specific studies on this topic are required.

Data by Shorvon[122] have shown that depression and cognitive dysfunction may be the result of a rapid dose escalation of topiramate. Obviously, slow titration of topiramate should be used to avoid the occurrence of these adverse events.

6.7 Gabapentin

Gabapentin is currently used as add-on therapy for the treatment of partial and generalised tonic-clonic seizures. Structurally, gabapentin is a cyclic GABA analogue and exerts influence on GABAergic neurotransmitter systems, especially GABA turnover.[75,123]

Clinical reports of patients with epilepsy treated with gabapentin generally indicate a mood improvement in tandem with a decreased level of depression and anxiety.[124-128] Such a favourable psychotropic profile for gabapentin seems to be promising for suicidality prevention, although the specific data in this domain are absent. The meticulous statistical analysis (with numerous psychometric scales) performed by Harden et al.,[125,126] revealed a significant influence exclusively on dysthymia, but not on depression or anxiety. This implies a subtleness, but not a magnitude, of gabapentin effect because dysthymia represents a mild depressive state that is quite different from major depression.[75]

Gabapentin also exerts beneficial effects on cognition in patients with epilepsy[72-74] and in healthy volunteers in comparison with carbamazepine.[129] Gabapentin had certain advantages over carbamazepine in 26% of assessed neuropsychological variables. In line with these data are findings on better gabapentin tolerability compared with carbamazepine in elderly patients.[74,130]

Interestingly, gabapentin has been shown to exert some efficacy in the management of social phobia, panic disorders and major affective disorders, i.e. in the treatment of affective spectrum disorders.[131] However, its efficacy against recurrent (unipolar) depression seems to be exaggerated. Thus, the findings of a randomised, placebo-controlled study by Frye et al.[132] indicated that gabapentin turned out to be ineffective in the treatment unipolar depression.

Gabapentin efficacy in the treatment of the broad spectrum of affective and anxiety disorders certainly implies the definite anxiolytic and thymoleptic properties of gabapentin. This, in turn, implies that it might be useful in the treatment of epileptic patients with high suicidality risk, although again the relevant data are absent. On the other hand, a certain similarity can be seen between gabapentin psychotropic effects and the effects of SSRIs, although gabapentin does not exert an influence on serotonergic receptors. All this is yet to be explained thoroughly.

In summary, gabapentin seems to be drug with certain positive psychotropic effects, as has been demonstrated in numerous studies on its efficacy in affective spectrum disorders and in patients with epilepsy. Obviously, such a positive psychotropic profile of gabapentin may be useful in epilepsy patients with a high risk for suicidality, and affective and behavioural disturbances. However, the primary efficacy of gabapentin concerned mostly dysthymia or mild forms of mood disorders, whereas in more severe cases its efficacy has yet to be proven. This implies that in epileptic patients with depression of a severe degree and suicidality, the additional administration of antidepressants is needed.

6.8 Tiagabine

Tiagabine is a GABA uptake inhibitor that prolongs the GABA presence in the synapses.[133] By that mechanism, tiagabine exerts its anticonvulsant effect. Tiagabine does not bind to catecholamine, acetylcholine, serotonin, histamine, opiate, glycine

or glutamate receptors.[133] The drug is indicated mostly for the management of patients with intractable partial epilepsy in an add-on regime.[134] Cognitive adverse effects of tiagabine in epilepsy treatment were, as a rule, not frequently registered.[135,136]

Thus, in a study by Fritz et al.,[137] tiagabine and topiramate were compared in terms of their efficacy and cognitive adverse effects. Both drugs have shown approximately equal efficacy, although differences in their influence on cognitive functions were revealed.

Tiagabine, unlike topiramate, did not have any influence on frontal-lobe associated functions (tests on verbal fluency, language comprehension, working memory and visual block tapping). Tiagabine had a negative effect on verbal memory only and, therefore, had advantages over topiramate. This would imply a more favourable profile of tiagabine in terms of influence on mood and suicidality, although the special studies on this issue have not yet been carried out. Nonetheless, in several placebo-controlled studies, increased nervousness and depressive mood were observed.[138,139] In this context, nervousness is believed to be a prominent tiagabine-related phenomenon.[75,138] The findings of Grabowska-Grzyb et al.[139] on the whole are consistent with these observations. The authors reported that tiagabine was more frequently used in epilepsy patients with depression than in patients without depression (14% vs 5%; $p < 0.05$), and regarded this drug as a risk factor in development of depression. Data concerning tiagabine suicidality provoking properties are not available, but in cases of severe nervousness physicians should be aware of a possible transformation from nervousness to suicidality.

6.9 Vigabatrin

Vigabatrin represents another GABAergic AED that inhibits the GABA breakdown.[140] Data on behavioural and cognitive effects of vigabatrin are controversial. Thus, the absence of any negative influence on cognition was reported in several trials.[74,141] On the other hand, some data suggest vigabatrin causes negative mood changes in patients with epilepsy.[16,74,141] Depression was registered in 5.1%, whereas psychosis was registered in approximately 1.1% of 2682 vigabatrin-treated patients.[10]

In the study by Grabowska-Grzyb et al.,[139] vigabatrin was much more frequently administered to patients with concomitant depression compared with patients without depression (30% vs 8%; $p < 0.05$). The data concerning vigabatrin influence on suicidality are still absent.

6.10 Lamotrigine

Lamotrigine is the oldest drug among the new generation of AEDs. The main mechanism of lamotrigine action is thought to block voltage-dependent sodium and calcium channels and thereby prevent excitatory glutamate release.[73,74,142] This mode of action is quite similar to that of carbamazepine,[75] although (unlike carbamazepine) lamotrigine is effective not only against partial and secondary generalised seizures, but primary generalised seizures as well.[75] The inhibition of glutamate and aspartate release by lamotrigine, according to a paradigm by Ketter et al.,[51] seems to be the principal mechanism of antidepressant efficacy of lamotrigine. Interestingly, lamotrigine exerts weak influence on serotonin reuptake in human plates and rat-brain synaptosomes *in vitro*[141-143] and, therefore, it shares common features with carbamazepine, valproate and zonisamide.

The favourable profile of lamotrigine psychotropic effects has been proven in numerous studies carried out in healthy volunteers and in patients with epilepsy. As a whole, no adverse cognitive effects were revealed after lamotrigine treatment.[73-75] Lamotrigine-treated patients showed much better results on attention, memory, affective symptoms and items of quality of life scales.[73-75]

Mood improvement is thought to be the most prominent among lamotrigine positive psychotropic effects.[144-146] Thus, in the study by Edwards et al.,[146] lamotrigine was compared with valproate in their influence upon mood disorders by using the Profile of Mood States (POMS), the BDI and Cornell Dysthymia Rating Scale. Interestingly, patients treated by lamotrigine had 21% improvement in

BDI, whereas POMS scores have shown improvement in several scales, including depression (33%), anger (30%), tension (27%) and total score (37%) compared with baseline level.

In a study by Cramer et al.,[147] lamotrigine was used as adjunctive medication to other AEDs in 155 epileptic patients with poorly controlled seizures. The authors could confirm mood improvement to a clinically significant degree despite the presence of other AEDs. They concluded that this effect was not likely to have been caused by synergy with other AEDs, but was rather attributed strictly to lamotrigine itself because it remained stable after withdrawal of the other AEDs.

In another study by Cramer et al.,[148] the improvement in the quality of life of patients with epilepsy after the conversion to lamotrigine monotherapy was demonstrated. The authors assessed the quality of life in patients with epilepsy who had previously been treated with either phenytoin or carbamazepine and were subsequently switched to lamotrigine monotherapy by use of the Quality of Life in Epilepsy (QOLIE)-31 scale. The total QOLIE-31 scores increased 10.7 points for patients rated by physicians as having mild improvement, and 17 points for patients having moderate or marked improvement. Nevertheless, the authors concluded that positive changes in quality of life are independent of seizure reduction. It assumes again the positive effect of lamotrigine on mood, which *a priori* could reduce the risk for suicidal behaviour.

Kockelmann et al.[149] compared the cognitive profile of lamotrigine and topiramate in patients with epilepsy receiving AED polytherapy and revealed lamotrigine superiority on several cognitive tests. After controlling for multiple comparisons, differences between lamotrigine- and topiramate-treated patients remained significant ($p < 0.0022$) for verbal fluency, verbal digit, visual block spans and nonverbal working memory, whereas for visual anticipation speed, planning ability, verbal working memory, verbal comprehension and mental rotation a nonsignificant trend towards differences was observed.

Looking at all these data together, the suggestion could be made that lamotrigine exerts positive psychotropic influence on both mood and cognitive functions, which could imply its preventive efficacy against suicidal behaviour, although specific data on suicidality and lamotrigine are not available.

6.11 Levetiracetam

Levetiracetam is regarded as the newest AED and is now approved for the treatment of partial seizures in add-on therapy and as monotherapy all over the world. Unfortunately, the exact levetiracetam mechanisms of action are not yet known and its psychotropic effects have yet to be studied thoroughly.

In a review by Cramer et al.,[150] increased levels of depression, nervousness, hostility, emotional lability and anxiety were reported. Devinsky and D'Esposito[67] had similar findings and stressed that approximately 10% of adults and 25% of children receiving levetiracetam exhibited irritability, anxiety, depression and other behavioural problems that, in turn, were seen more often in patients with developmental delays. All these symptoms may lead to suicidality if they are not recognised and treated in time.

The existence of suicidal thoughts with levetiracetam is actually well recognised and was discussed by French et al.[151] and Mula et al.[152] Clinicians should be more attentive to affective disturbances in patients with epilepsy during novel AED administration.

6.12 Zonisamide

Zonisamide shares multiple mechanisms of action with topiramate: blockade of voltage-dependent sodium channels, blockade of calcium channels and GABAergic action. Like topiramate, zonisamide inhibits carbonic anhydrase, but unlike the former has influence on serotonin turnover in striatal and hippocampal brain regions.[153,154] Psychotropic properties of zonisamide have not been properly studied yet, and available reports on this issue are entirely contradictory. Thus, in the pooled data of placebo-controlled studies the more frequent incidences of

Table II. The influence of antiepileptic drugs (AEDs) on mood, cognitive functions and suicidality[a]

AED	Mood	Cognitive functions	Suicidality
Phenobarbital	↓[54-63]	↓[54-63]	↑[9,10,58]
Phenytoin	↓[66,67,69]	↓[66,67,69]	↑ F, ↑M[9,10]
Carbamazepine	↑[83-85]	↑[90,91]	↓F, M?[9,10]
Oxcarbazepine	↑[88]	↓,[89,93,94]↑ [90,91]	↓?
Valproate	↑[75,99-104]	↑[73,74,90,91,105-107]	↓F, M?[9,10]
Topiramate	↓[72-75,115,116]	↓[112-114]	↑?[121]
Gabapentin	↑[124-128]	↑[72-74,129]	↓?
Tiagabine	↓[75,138,139]	↓[135-137]	NA
Vigabatrin	↓[16,139,141]	NE	NA
Lamotrigine	↑[144-148]	↑[73-75,148]	↓?
Levetiracetam	↓[150]	↓[150]	↑[151,152]
Zonisamide	↓?[155,156]	↓? [155,156]	NA

a AEDs with mood improvement and probable antisuicidal properties are marked in boldface.

F = female; **M** = male; **NA** = data are not available; **NE** = no effect; ↑ indicates increase; ↓ indicates decrease; ↑**?** indicates possible increase; ↓**?** indicates possible decrease.

irritability, depression, anxiety, paranoia and hallucinations during zonisamide therapy in comparison with placebo were revealed. Moreover, psychotic episodes that met the *International Classification of Diseases* (10th Edition) criteria for organic delusional disorder and organic hallucinosis also developed in 14 patients treated by zonisamide.[155,156] Sedation and mild sleepiness were also observed during zonisamide administration.[155,156] Data on possible zonisamide influence upon suicidality are not available.

7. Discussion

Three principal hypotheses form the cornerstones of the current article.

First, suicidality in patients with epilepsy should be regarded in association with depression, personality disorder and cognitive impairment, which, in turn, may not have a common neuropsychological basis. In other words, suicidality in epilepsy does not represent a single isolated phenomenon, but rather is a part of more complex syndrome. Thus, cognitive deterioration and depression in patients with epilepsy should warn clinicians of a high risk of suicidality.

Secondly, all AEDs differ in their mechanisms of action, and any that provoke depression and cognitive deterioration in patients with epilepsy should be regarded as drugs with a potential risk for suicidality.

Thirdly, since serotonergic mechanisms are involved in the pathogenesis of depression with suicidal behaviour and epilepsy itself, AEDs with serotonergic properties should reduce the suicidality risk because they exert effects similar to antidepressants such as SSRIs.

The analysis of numerous data has convincingly shown that different AEDs have differences not only in their mechanisms of action, but also in their influences on cognition and mood in patients with epilepsy. The main data on AED psychotropic effects and suicidality are summarised in table II. As has been shown, phenobarbital and phenytoin are the only two AEDs that decrease mood and cognitive functions and increase suicidality at the same time. Similarly, topiramate also decreases mood and cognition, but its influence upon suicidality has not been proven in evidence-based trials. On the other hand, carbamazepine, oxcarbazepine, valproate, gabapentin and lamotrigine are characterised by favourable effects on mood, cognition and suicidality. Carbamazepine and valproate have been found to exert antisuicidal effect in patients with epilepsy,[9,10] whereas lamotrigine, oxcarbazepine and gabapentin supposedly may prevent suicidality because they improve mood and cognitive functions.

Until now, only the hypothesis of Ketter et al.[51] has been proposed to explain the positive and negative psychotropic effects of different AEDs.[51] In this model, only GABAergic and antiglutamatergic mechanisms have been included; other possible mechanisms that could explain the differences between the AEDs in terms of their psychotropic effects have not been incorporated. Furthermore, the opposition of sedating and anxiolytic properties on the one hand and activating and antidepressive properties on the other hand seems to be rather artificial and hardly true, because depression and anxiety are frequently seen together in cases of psychiatric comorbidity. Moreover, carbamazepine and oxcarbazepine have not been included in Ketter's hypothesis. Although both drugs are devoid as GABAergic and antiglutamatergic mechanisms, they possess certain positive psychotropic effects.

Obviously, as suggested by Ketter et al.,[51] two components of the complex antiepileptic activity of different AEDs are not enough to thoroughly explain the possible mechanisms of the broad spectrum of psychotropic effects seen with these agents, including any antidepressive and antisuicidal properties of AEDs.

Interestingly, among five AEDs with antisuicidal properties, at least three drugs (carbamazepine, valproate and lamotrigine) definitely, and oxcarbazepine supposedly, possess serotonergic activity, as can be seen from table III. The influence on serotonin receptors seems to be once again a mechanism that has not been taken into consideration to explain the positive psychotropic effects of AEDs, including antisuicidal properties. Therefore, in order to explain all the psychotropic effects of AEDs and their influence on suicidality, Ketter's paradigm should be supplemented by an understanding of the serotonergic mechanisms of AEDs, although this proposition remains to be proven in studies.

8. Conclusion

This review has covered a broad range of problems on suicidality risk factors in epilepsy patients with special emphasis on AEDs. Patients with epilepsy have increased risk for suicidality. Suicidality in patients with epilepsy should be regarded only as one facet of more complex neuropsychiatric syndrome, including depression and personality deviations coupled with cognitive impairment. AEDs may interact with nonpharmacological risk factors and by that can provoke suicides. Some AEDs have prosuicidal properties, whereas others exert antisuicidal effects.

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Table III. Modes of action of antiepileptic drugs (AEDs)[a]

AED	Na^+ channels	Ca^{2+} channels	GABA	Glutamate	Serotonin
Phenobarbital	−	−	+	−	−
Phenytoin	+	−?	−	−	−
Carbamazepine	+	−	−	−	+
Oxcarbazepine	+	+	−	−	+?
Valproate	+	+	+	−	+
Topiramate	+	+	+	+	−
Gabapentin	+	?	+	−	−
Tiagabine	−	−	+	−	−
Vigabatrin	−	−	+	−	−
Lamotrigine	+	+	−	+	+
Levetiracetam	−	+	−	−	−
Zonisamide	+	+	−	−	+

a AEDs with mood improvement and probable antisuicidal properties are marked in boldface.

+ indicates proven effect; **−** indicates lack of effect; **+?** indicates questionable effect; **−?** indicates questionable lack of effect.

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